

developmental therapeutics

4580 SAFETY, PHARMACOKINETICS, AND EFFICACY OF RECOMBINANT HUMAN (RH)APO2L/TRAIL IN COMBINATION WITH PACLITAXEL, CARBOPLATIN, AND BEVACIZUMAB (PCB) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): RESULTS OF A PHASE 1B STUDY

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rhApo2L/TRAIL is a pro-apoptotic receptor agonist (PARA) that activates death receptors DR4 and DR5, selectively inducing apoptosis in cancer cells. rhApo2L/TRAIL was well tolerated and demonstrated antitumor efficacy in the first-in-human (FIH) study (Herbst et al. JCO 2006; 24: abstract 3013). The objectives of this ongoing study (n = 24 pts) were to determine the maximum tolerated dose (MTD) of rhApo2L/TRAIL (up to target doses indicated below) in combination with PCB and the pharmacokinetics (PK) of rhApo2L/TRAIL. Eligible pts were ≥ 18 years with stage IIIB/IV untreated NSCLC and an ECOG score of 0 or 1. rhApo2L/TRAIL was administered IV at 4 or 8 mg/kg/day on days 1-5, or at 15 or 20 mg/kg/day on days 1-2 of each 21-day cycle. P (200 mg/m²), C (AUC = 6), and B (15 mg/kg) were given on day 1 of each cycle. As of 11 Feb 08, all 24 pts received ≥ 1 dose of rhApo2L/TRAIL + PCB (6 in each of the 4 cohorts). 12 pts were men, median (range) age was 54 (42-73) years, 21 had stage IV disease, and 13 had ECOG of 1. There were no dose-limiting toxicities. Adverse events possibly related to rhApo2L/TRAIL were reported in 23 pts and included rhinitis, arthralgia, epistaxis, hypercholesterolemia, hypertriglyceridemia, and myalgia, each in ≥ 5 pts. Three pts each had transient grade 2 transaminase elevations (ALT, AST; no CTCAE grade ≥ 3). Two pts had grade 2 bilirubin elevations (no grade ≥ 3). All pts have completed treatment and 15 pts remain in long-term follow-up, 18 pts completed all 6 cycles of therapy. rhApo2L/TRAIL PK values (C_{max}, AUC, t_{1/2}) were similar to the FIH study (Ling et al. JCO 2006; 24: abstract 3047). To date, no effect of rhApo2L/TRAIL on PK of P, C, or B has been observed. The overall tumor response rate was 58%: 14 of 24 pts had confirmed responses (13 partial, 1 complete). Nine pts had stable disease (7 ≥ 12 weeks); 1 pt had disease progression. In conclusion, rhApo2L/TRAIL plus PCB appears to be well tolerated and has promising anti-tumor activity in this patient population. A randomized phase 2 trial is ongoing in bevacizumab-eligible and -ineligible patients with advanced NSCLC.

4590 DENOSUMAB IN PATIENTS WITH BONE METASTASES FROM CASTRATION-RESISTANT PROSTATE CANCER AND ELEVATED BONE RESORPTION DESPITE INTRAVENOUS BISPHOSPHONATE (IV BP) THERAPY: ANALYSIS OF A RANDOMISED PHASE II TRIAL

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Bone metastases in prostate cancer (CaP) are usually described as osteoblastic (bone forming), but also have a prominent osteolytic (bone destroying) component that results in elevated bone resorption markers, such as urinary N-telopeptide (uNTx). Elevated uNTx levels are associated with skeletal-related events (SREs), disease progression, and death. Bone resorption is mediated by osteoclasts, whose formation, function, and survival depend on the receptor activator of NF-κB ligand (RANKL). Denosumab, a fully human monoclonal antibody, inhibits RANKL to reduce osteoclast-mediated bone destruction. In this study, the effects of denosumab in patients with bone metastases and elevated uNTx (> 50 nM/mM creatinine [Cr]) while receiving IV BPs were evaluated. Patients were randomised to continue IV BPs every 4 weeks (Q4W) or change to subcutaneous denosumab 180 mg Q4W or 180 mg Q12W.

The primary endpoint was the percentage of patients achieving uNTx < 50 nM/mM Cr (uNTx < 50) at week 13. Of the 111 enrolled patients, 45% had CaP, 41% had breast cancer, and 14% had multiple myeloma or other solid tumors. Among patients with CaP, 69% (22/32) in the denosumab arms achieved the primary endpoint of a uNTx < 50 at week 13, compared with 19% (3/16) of the IV BP cohort (p < 0.001). At week 25, the proportion of patients with CaP who achieved a uNTx < 50 was 69% in the denosumab arms and 31% in the IV BP cohort (p = 0.014). All CaP patients in the IV BP group received zoledronic acid. The effect of denosumab on normalisation of uNTx levels was similar for patients with moderate (50 - 100 nM/mM Cr) and high (> 100 nM/mM Cr) screening uNTx. The incidence of SRE was 3% in the denosumab arms and 19% in the IV BP arm. Rates of adverse events were similar between treatment groups. One serious adverse event (hypophosphatemia), possibly related to denosumab, was reported. In metastatic CaP, a greater proportion of patients treated with denosumab achieved normalisation of bone resorption markers than those who continued receiving IV BPs. Phase III trials of denosumab for prevention and treatment of skeletal complications of bone metastases are in progress.

4600 HEPATOCYTE GROWTH FACTOR (HGF) IS A PROGNOSTIC BIOMARKER FOR OVERALL SURVIVAL AND A PHARMACODYNAMIC BIOMARKER OF SORAFENIB RESPONSE IN THE SHARP PHASE III HCC TRIAL

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Objective: HGF is the ligand for cell surface RTK c-Met. c-Met signaling is implicated in several cancers, including HCC. c-Met signals in part through the Ras/Raf pathway, which led to the investigation of HGF as a potential pharmacodynamic/response biomarker for sorafenib action. We performed a pharmacodynamic assessment of the randomized, controlled, double-blind, SHARP trial, in which sorafenib (Nexavar), a multikinase inhibitor, significantly improved overall survival (Llovet J, 2007).

Methods: patients with advanced HCC (n=602) were randomized to receive either sorafenib or placebo. ELISA for HGF was performed on plasma samples collected at baseline (BL) and after 12 weeks of treatment (C3D1).

Results: Plasma HGF data were available for 81% of patients. Elevated levels of HGF at BL correlated with poor overall survival (OS) in a univariate analysis of patients in the placebo group only (P=0.013, n=251). Patients in the placebo group with high HGF (>3279 pg/mL or 75th percentile; n=72) had OS of 160 days compared to 297 days for those with low HGF (<3279 pg/mL; n=179). In sorafenib-treated patients, mean intra-subject HGF levels decreased at C3D1 (compared to BL) by 285.0 pg/mL (7.4%, P<0.001), while mean levels increased in the placebo cohort by 371.0 pg/mL (16.3%, P<0.001). This C3D1 change from BL in the sorafenib group was significantly different from that in the placebo group (P<0.0001). HGF decreased in 74.3% of sorafenib-treated patients, compared with an increase in 68.8% of patients in the placebo group. Sorafenib-treated patients with large C3D1 decreases in HGF (more than 294.0 pg/mL [median]) had longer TTP than those without such a large decrease (253 vs 177 days, P=0.029). However, a similar correlation was not seen with OS.

Conclusions: HGF appears to be a prognostic biomarker for OS in patients with HCC. HGF was also a pharmacodynamic marker that responded to treatment with sorafenib, and the magnitude of the C3D1 change in HGF level in sorafenib-treated patients correlated with TTP. These results provide a molecular rationale for the clinical investigation of sorafenib in combination with HGF/c-met inhibitors for the treatment of HCC.

4610 CORRELATION OF OUTCOME AND TUMOUR IMAGING PARAMETERS WITH CIRCULATING BIOMARKERS OF SUNITINIB MALATE IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: Antitumour activity in patients (pts) with hepatocellular carcinoma (HCC) has been demonstrated with the multikinase inhibitor, sunitinib malate (SU) (Faivre et al. ASCO 2007). This study investigated plasma levels of soluble (s) proteins (VEGF-A, VEGF-C, sVEGFR-2 and -3, and sKIT) with roles in angiogenesis and SU target pathways as potential as biomarkers of SU activity.

Methods: 37 pts received SU 50 mg/d for 4 wks on, 2 wks off, every 6 wks. Pre-dose plasma samples were taken on days (D) 1, 14, and 28 of cycle (C) 1 and D1 and 28 of C2. Soluble protein levels were measured by ELISA. Baseline levels and changes from baseline were analysed for association with efficacy measures (time to progression [TTP], overall survival [OS], objective response, and tumour density changes [Choi criteria]).

Results: In most pts, plasma protein levels were modulated during treatment. By the end of C1, sVEGFR-2 and -3 and sKIT levels decreased by ~50%, 70%, and 30%, respectively, and VEGF-A levels increased >3-fold relative to baseline. VEGF-C levels decreased by 30% by the end of C2. Pretreatment VEGF-C levels correlated with TTP and OS, with levels above the median (>822 pg/mL) associated with longer times (TTP, p=0.004; OS, p=0.05). Pretreatment VEGF-C levels were also significantly higher in pts with partial response or stable disease >3 months (n=14) vs pts with progressive disease (n=13; p=0.02). Pts with largest decreases in sKIT (< median) at CID14 had longer TTP (p=0.018); sKIT decreases also correlated with response according to Choi criteria (p=0.019) and with higher tumour necrosis, based on volumetric measurement (p=0.02; n=21). Larger increases in VEGF-A (p=0.03) and larger decreases in sVEGFR-2 correlated with higher tumour necrosis (p=0.036).

Conclusions: SU therapy is associated with modulation of plasma proteins involved in VEGF and KIT pathways in HCC pts. The strongest correlation with outcome was demonstrated by baseline VEGF-C. Additional correlations between biomarkers and various measures of antitumour activity were observed. In HCC, analysis of these biomarkers in larger studies of SU may be warranted.

462PD INTERIM RESULTS FROM A PHASE 1B STUDY OF SAFETY, PHARMACOKINETICS (PK) AND TUMOR RESPONSE OF THE ANGIOPOIETIN1/2-NEUTRALIZING PEPTIDOMIMETIC AMG 386 IN COMBINATION WITH AMG 706, BEVACIZUMAB (B) OR SORAFENIB (S) IN ADVANCED SOLID TUMORS

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Objective: AMG 386, an investigational selective angiopoietin1/2-neutralizing peptidomimetic inhibits angiogenesis by blocking angiopoietin binding to Tie2 receptors. This ongoing open-label study assesses safety including immunogenicity, PK and tumor response (per RECIST) of AMG 386 when combined with other angiogenesis inhibitors.

Methods: Adult patients (pts) with documented advanced solid tumors receive either 3 (n=6) or 10 mg/kg (n=9) of AMG 386 IV QW plus B 15 mg/kg IV Q3W (AMG 386+B); or 3 mg/kg of AMG 386 IV QW plus either 75 (n=8) or 125 mg (n=3) of AMG 706 orally QD (AMG 386+706); or (pts with renal cell carcinoma) either 3 (n=3) or 10 mg/kg (n=7) of AMG 386 IV QW plus S 400 mg orally BID (AMG 386+S). AMG 386 treatment starts on day 8; all other on day 1.

Results: 46 pts are enrolled, receiving ≥1 dose of AMG 386 (AMG 386+B/706/S n=25/11/10). 61% of pts experienced AMG 386 treatment-related adverse events (AEs), of which 82% were gr ≤2. See Table for related AEs of specific interest. 2 fatal hemorrhagic events (squamous cell head and neck carcinoma) occurred in the AMG 386+B group; both were deemed possibly AMG 386-related. No related thromboembolic events or gr ≥3 hypertension occurred. Combining treatments did not markedly affect the PK profiles of AMG 386 and the other agents, but large variability was seen. 13 (36%) of 36 tested pts had anti-AMG 386 binding antibodies (all non-neutralizing), which did not appear to affect AMG 386 exposure. There were 5 confirmed PRs: AMG 386+B/706/S n=2/1/2 (duration of response, range: 16-76 wks). 23 pts achieved SD: AMG 386+B/706/S n=14/4/5 (SD >6 months n=9); 9 pts had PD.

Conclusions: Combining AMG 386 with AMG 706, B or S was tolerable, had no marked effect on their PK profiles, and showed promising tumor response. Updated data from all cohorts will be presented. Treatment-related AEs of specific interest.

AE, n (%)	AMG 386+B N=25		AMG 386+706 N=11		AMG 386+S N=10	
	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
Any AE	13 (52)	2 (8)	6 (55)	1 (9)	9 (90)	2 (20)
Diarrhea	2 (8)	0	3 (27)	1 (9)	5 (50)	1 (10)
Weight decreased	1 (4)	0	0	0	3 (30)	1 (10)
Hypophosphataemia	0	0	0	0	1 (10)	0
Proteinuria	0	0	0	0	1 (10)	0
Rash	1 (4)	0	0	0	1 (10)	0
Hypertension	1 (4)	0	1 (9)	0	6 (60)	0
Hemorrhage	2 (8)	2 (8)	1 (9)	0	0	0

463PD PHASE (PH) I/II STUDY OF THE HISTONE DEACETYLASE INHIBITOR BELINOSTAT (BEL) IN COMBINATION WITH CARBOPLATIN (CA) AND PACLITAXEL (P) IN ADVANCED SOLID TUMORS (PH I) AND RELAPSED OVARIAN CANCER (PH II)

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Bel is synergistic with Ca and P in preclinical models, including ovarian cancer. This study assesses safety and activity of the BelCaP combination.

Methods: In ph I, cohorts of 3-6 patients (pts) were treated with escalating doses of Bel as a 30-min infusion daily for 5 days (d) together with standard dose Ca and/or P (on d 3) every 3 weeks. In ph II, pts were treated with Bel 1000 mg/m²/d, d 1-5, Ca AUC 5 d 3, and P 175 mg/m² d 3.

Results: In ph I, 23 pts were treated with a median of 4 cycles (range 1 – 28+) in 3 cohorts with Bel 600 mg/m²/d (BelCa, BelP, BelCaP), and BelCaP with Bel 800 and 1000 mg/m²/d. No dose-limiting toxicity was observed. Drug-related adverse events (AE) were nausea and fatigue with no related grade 4 AE, and grade 3 non-hematological AE in more than one pt was peripheral sensory neuropathy (n=2). Most common grade 3/4 laboratory abnormality was neutropenia (26% of pts). 2 pts had partial responses (PR): 1 with rectal cancer (3 prior therapy lines) and 1 with pancreatic cancer (prior gemcitabine). Median treatment duration for 11 pts with stable disease (SD) was 116 d (range 43 to +592 d); 4 pts received > 10 cycles (unknown primary, bladder, melanoma, Ewings sarcoma).

Ph II enrolled 35 patients with epithelial ovarian cancer (median 3 prior regimens; range 1-4). Recruitment was completed in Dec 2007 with 11 pts currently on therapy. Most common related AE were nausea (80%), fatigue (73%), vomiting (63%), and diarrhea (27%); most common related grade 3/4 AE were neutropenia (n=4), transaminitis (n=4), and fatigue (n=3). Preliminary efficacy, defining platinum sensitivity by most recently received platinum therapy, include 4 PR and 12 SD in platinum-resistant pts with platinum-free interval (PFI) < 6 mo (n=21); in the subgroup with PFI < 3 mo (n=13), there were 2 PR and 8 SD. There was 1 CR and 9 PR in platinum-sensitive pts with PFI > 6 mo (n=14). In total, 1 CR and 13 PR have been observed.

Conclusions: BelCaP is well-tolerated and shows clinical activity in heavily pre-treated pts with advanced solid tumors, as well as in pts with platinum-sensitive and resistant ovarian cancer.

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464PD EFFECT OF AXITINIB (AG-013736) ON FATIGUE, THYROID STIMULATING HORMONE (TSH), AND BIOMARKERS: RESULT FROM A PHASE I STUDY IN JAPANESE PATIENTS

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Background: Axitinib is an oral, potent and selective inhibitor of VEGF receptors 1, 2, and 3. A Phase I study of axitinib has been conducted in Japanese patients with solid tumors to evaluate safety and pharmacokinetics (PK) as well as effects on TSH and biomarkers. In addition, pharmacodynamic evaluation using FDG-PET was performed in selected patients.

Methods: Twelve patients with advanced solid tumors were enrolled and received 5 mg BID of axitinib. PK, biomarkers (VEGF, soluble [s] VEGFR2, sVEGFR3, and sKIT) and TSH (weekly or every 2 weeks) were investigated.

Results: Dose-limiting toxicities were observed in one patient (grade [G] 3 proteinuria and G3 fatigue); the fatigue was associated with elevation of TSH. Common drug-related adverse events were fatigue (83%), diarrhea (75%), anorexia (67%), stomatitis (58%), elevation of TSH (58%). Five patients developed G3 fatigue, and TSH was elevated in 4 of these patients. The elevation of TSH was generally observed within one month after the start of treatment, and the time course of TSH and fatigue appeared to be related. In preliminary analyses, abnormal TSH was highly correlated with exposure to axitinib (r=0.85) except for 2 patients whose TSH at baseline was abnormal. Axitinib consistently decreased sVEGFR2 (-35%) and sVEGFR3 (-46%), and increased VEGF (+288%) in plasma after one month of axitinib treatment, suggesting selective pharmacodynamic activity against VEGF and its receptors.

Decrease in sVEGFR2 levels was significantly correlated with exposure to axitinib ($r=-0.89$). Tumor size was decreased in 9 patients. Stable disease (SD) ≥ 24 weeks was observed in 4 patients (colorectal cancer: 2 patients, non-small cell lung cancer [NSCLC]: 1 patient, thymic cancer: 1 patient) and was ≥ 40 weeks in 1 NSCLC patient. FDG-PET was performed in 9 patients, and SUVmax was decreased in 8 patients.

Conclusions: Following axitinib administration, fatigue and abnormal TSH were frequently observed. There was a significant correlation between sVEGFR2 and TSH vs exposure to axitinib. The dose of 5 mg BID was well tolerated and considered as a recommended starting dose for Japanese patients.

465PD INCIDENCE OF RENAL TOXICITY WITH ANTIANGIOGENIC THERAPIES DEVELOPED IN PHASE I TRIALS

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Background: Antiangiogenic therapies have demonstrated their efficacy in a variety of metastatic solid tumors. Several phase I trials are currently evaluating new anti-angiogenic compounds. Hypertension and proteinuria are classical side-effects of this class of agents. However, there's scant data about acute renal failure (ARF) and serum creatinine (Cr) variations in patients (pts) treated with new anti-angiogenic compounds in phase I trials.

Patients and methods: Between November 2005 and March 2008, 72 pts with solid tumors were included in four Phase I protocols: 32 pts received pan-HER/VEGFR inhibitor (A), 29 pts received a vascular-disrupting agent (B) and 11 pts received pan-VEGFR inhibitor in combination with CPT11 (C). For each pt we analysed retrospectively serum Cr, clearance of Cr (CLCR) calculated by both Cockcroft and Gault (CICG) and aMDRD equation at baseline, during treatment and at the end of treatment. Acute renal failure (ARF) was defined by a decrease of CrCl $> 25\%$, and severe ARF by a decrease of CrCl $> 50\%$. Chronic renal failure (CRF) was defined according to the International nephrology society guideline. A renal dysfunction was defined by a Cr < 60 ml/min with normal Cr ($< 125 \mu\text{mol/l}$).

Results: Each pt received an average of 4 cycles of treatment (1 to 12). Baseline CRF incidence was 12.5%. ARF frequency varied from 41.7 to 44.4% (A = 18/32, B = 12/29, C = 0/11) during treatment. Seven to 9.7% among these were severe (A = 4/32, B = 1/29, C = 0/11). Moreover, 16 to 18% of pts remained renal insufficient at the end of the study (A = 6/32, B = 6/29, C = 0/11). From the start till the end of treatment, 25% and 10% clearance reduction were noted for 20% and 50% of pts, respectively. Under treatment, the incidence of undiagnosed renal dysfunction was 12.5%. Average of clearance reduction was 10 ml/min/1.73m² between baseline and end of treatment.

Conclusion: Renal toxicity incidence in phase I patients treated with anti-angiogenic compounds was much higher than expected. Simple screening of Cr levels appears as insufficient and careful nephrological monitoring at baseline and during treatment should be implemented in early clinical trials assessing the risk/benefit ratio of new anti-angiogenic compounds.

466PD FUNCTIONAL IMAGING BY DCE-US FOR EARLIER EVALUATION OF TARGETED THERAPIES : WHICH PARAMETER TO EVALUATE IT?

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Background: The early evaluation of targeted treatments is a major challenge in oncology. Functional approaches based on the measurement of tumoral vascularization have been developed using different modalities of imaging (CT, MRI, US). We analyzed the response of tumors in three studies using different targeted treatments with dynamic contrast enhanced-ultrasonography (DCE-US). Seven parameters characterizing tumor perfusion were estimated. The objective of the study was to determine which parameter is the most appropriate to confirm earlier the efficacy of treatment.

Methods: A total of 558 DCE-US were performed in 75 patients included in 3 following studies (multikinase inhibitor targeting angiogenic-receptor with a cytotoxic or tyrosine-kinase inhibitor targeted angiogenic-receptor and C-kit). Each DCE-US was performed using contrast agent (Sonovue, Bracco) with perfusion and quantification softwares (Toshiba) from raw linear data. Seven quantitative parameters of perfusion were estimated: peak intensity (PI) and area under the curve (AUC), area under the wash-in (AUWI), area under the wash-out (AUWO), time to PI, mean transit time (MTT), wash-in slope. DCE-US were performed before treatment and after D 8, 15, 21 (according each study design) and every 2 months. Patients were classified as good

responders and bad responders according the response (RECIST on CT-scan) after 2 cycles.

Results: Among the 7 parameters, the parameters related to the blood volume studies (AUC and peak intensity) were always earlier significant modified ($P=0.04$ to $P=0.004$). One was never modified: MTT. For the 4 others, it was dependent oneach study.

Conclusions: DCE-US is a sensitive tool to evaluate tumor response to targeted drugs. Functional parameters related to the blood volume are more pertinent and represent a key to add value to early evaluation of targeted therapies.

467PD CLINICAL SIGNIFICANCE OF CIRCULATING CELL DEATH BIOMARKERS (BM) IN SMALL CELL LUNG CANCER (SCLC) PATIENTS RECEIVING CHEMOTHERAPY

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Introduction: SCLC invariably relapses after chemotherapy, underlining the need for new therapies. Integration of blood-borne BM into early clinical trials may speed drug development. The M65TM and M30 apoptosisTM assays (Peviva) detect total and apoptotic cytokeratin 18 (CK18) specific to dying epithelium, whilst the Cell Death Detection kitTM (Roche) detects nucleosomal DNA (nDNA) shed from all dying cells. The utility of these assays in SCLC is unknown.

Methods: Samples from 63 chemonaive patients with SCLC were analysed for CK18 products (plasma) and nDNA (serum), serial samples were taken from 39 patients during the first cycle of standard chemotherapy (Day 1, 2, 3, 8 or 15 and 22) and clinical data were collected. BM values were log transformed and analysed using standard statistical methods.

Results: nDNA and total (M65), but not apoptotic (M30), CK18, were significantly higher in SCLC patients than 85 healthy controls (medians 1.19 vs 0.30 ($p<0.001$), 512 vs 245 U/L ($p<0.001$) and 235 vs 199 U/L (NS) respectively). M65 was higher in extensive disease (765 vs 360U/L $P<0.001$), patients with liver metastases (1173 vs 392U/L $P<0.001$) and correlated with LDH ($p<0.001$). In univariate analysis high baseline levels of M30, M65 and LDH were associated with poor overall survival ($P<0.001$). In multivariate analysis only M65 remained as an independent prognostic factor, HR = 2.11 (95%CI 1.2-3.44) p value < 0.005 . After chemotherapy BM peaked at 48 hr, then fell by day 22 mirroring tumour response. A rise in nDNA at 48 hr was associated with early response (mean change 46% vs -53% $p<0.05$), whilst a rise in M30 at 48 hr predicted severe toxicity (mean change 49% vs 14% $p<0.05$).

Conclusions: The clinical significance of these BMs in SCLC has not previously been reported on. Our data suggests that M65 is an independent adverse prognostic factor. In addition, nDNA can predict for response and M30 for toxicity when assessed 48 hours after cytotoxic therapy. These BM should be considered for integration into future trials of novel mechanism based therapies in SCLC.

468PD SAFETY AND PHARMACOKINETICS (PK) OF MOTESANIB DIPHOSPHATE WITH OR WITHOUT PANITUMUMAB (PMAB) PLUS FOLFIRI OR FOLFOX FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER (MCR)

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Objectives: Motesanib is an investigational, oral inhibitor of VEGF, PDGF and Kit receptors. Pmab is a fully human anti-EGFr antibody approved for the

treatment of mCRC. This ongoing phase 1b, open-label, dose-finding study establishes the safety of motesanib with or without pmab plus chemotherapy. Dose-limiting toxicities (DLTs), PK, and tumor response (every 6-8 wks from wk 6) are assessed.

Methods: Pts had mCRC, ECOG 0-1, ≤1 prior chemotherapy, and no prior oral anti-VEGFR or anti-EGFR therapy. Cohorts (C) received, based on prior therapy, either FOLFIRI (C1) or FOLFOX (C2) plus pmab (6mg/kg IV day 1 of each 2-wk cycle) and escalating doses of motesanib given continuously from day 3 of cycle 1; or, FOLFIRI (C3) or FOLFOX (C4) plus motesanib 125mg QD (see Table for dose cohorts).

Results: 56 pts are enrolled, receiving ≥1 dose of motesanib (C1/2/3/4 N=36/17/2/1). There were 9 DLTs (see Table). 51 pts had motesanib treatment-related adverse events (AEs): C1/2/3/4 n=32/16/2/1. Related AEs of interest include gr 3 hypertension (C1/2/3/4 n=2/1/0/0), gr 3 pulmonary embolism (n=2/0/0/0), gr 3 deep vein thrombosis (n=1/2/0/0), and gr 3 jugular vein thrombosis (n=0/1/0/0). There was 1 gr 4 (neutropenia; C2, 75mg QD) and 1 gr 5 event (sepsis; C1, 50mg QD). Preliminary data show that motesanib exposure at 50mg QD (FOLFOX) and 50-125mg QD (FOLFIRI) is not affected by concurrent administration of chemotherapy plus pmab. Motesanib did not markedly alter the PK profiles of irinotecan or its metabolites. There is 1 confirmed CR (C2), 22 confirmed PR (C1 n=15, 42%; C2 n=7, 41%), and 19 SD (C1 n=13, 36%; C2 n=6, 35%).

Conclusions: Motesanib is being investigated in combination with standard therapies for mCRC. Updated safety and efficacy data will be presented. Summary of DLTs.

Dose Cohorts	DLTs (all gr 3)
C1, n=36: FOLFIRI+pmab+motesanib 50mg, 75mg, 100mg, or 125mg QD; or 75mg BID	n=3: deep vein thrombosis (75mg QD), diarrhea (125mg QD), diarrhea/GI disorder (75mg BID)
C2, n=17: FOLFOX+pmab+motesanib 50mg, 75mg, 100mg, or 125mg QD; or 75mg BID	n=4: fatigue (n=2; 50mg QD), febrile neutropenia/diarrhea (75mg QD), hypokalaemia/diarrhea (75mg QD)
C3, n=2: FOLFIRI+motesanib 125mg QD	n=1: dyspnea
C4, n=1: FOLFOX+motesanib 125mg QD	n=1: congestive cardiomyopathy

469P A PHASE I DOSE-FINDING STUDY OF SUNITINIB (SU) IN COMBINATION WITH GEMCITABINE (G) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS

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Background: Sunitinib malate (SUTENT[®]) is an oral multi-kinase inhibitor with significant antitumor activity in renal cell carcinoma (RCC) and other cancers. This study assessed the maximum tolerated dose (MTD), safety, and pharmacokinetic (PK) profile of SU in combination with G in pts with advanced solid tumors.

Methods: Pts received escalating oral doses of SU (25–50 mg/day) on a 6-wk cycle (4 wks on, 2 wks off treatment; Schedule 4/2) with G (750–1250 mg/m²) IV over 30 min on Days 1, 8, 22, and 29. Subsequently, patients received SU on a 3-wk cycle (Schedule 2/1) with G on Days 1 and 8. Safety was evaluated using adverse event (AE) reports and laboratory tests. Objective response was assessed by RECIST, and PK data were analyzed at each dose level.

Results: 35 pts (most common tumors: RCC, n=20; pancreatic, n=11) received SU + G, including 8 pts on Schedule 4/2 and 27 pts on Schedule 2/1. Schedule 4/2 was not pursued beyond the initial dose level (SU 37.5 mg/day + G 750 mg/m²). On Schedule 2/1, MTD has not yet been reached, and enrollment continues at the highest dose level (SU 50 mg/day + G 1250 mg/m²). On Schedule 2/1, grade (Gr) 4 non-hematologic AEs included myocardial infarction (n=1) and pulmonary embolism (n=2), none considered related to study treatment. Gr 4 laboratory abnormalities included neutropenia (n=8), with no instances of febrile neutropenia, thrombocytopenia (n=1), increased lipase (n=7), and increased blood uric acid and potassium (n=2). Promising antitumor activity has been observed on both schedules across different dose levels, in pts with pancreatic or renal cancer. At all dose levels to date, the C_{max} and AUC of the drugs and their metabolites following combination therapy were similar to those for single-agent SU or G, indicating no clinically significant drug–drug interactions during co-administration.

Conclusions: Combination therapy with SU and G in pts with advanced solid tumors is well tolerated, does not result in significant drug–drug interactions, and is associated with promising antitumor activity. This combination will be studied further in disease-specific clinical trials.

470P SUNITINIB IN COMBINATION WITH CARBOPLATIN (C) PLUS PACLITAXEL (P) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS (STS): PHASE I STUDY RESULTS

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Sunitinib (SU), an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R and RET, has demonstrated antitumor activity in patients with advanced STs and is approved for the treatment of advanced RCC and imatinib-resistant/intolerant GIST. This study evaluated the safety and efficacy of SU in combination with carboplatin (C) plus paclitaxel (P) in STs.

Pts with advanced STs (not eligible for curative therapy) were enrolled. Serial pt cohorts were escalating daily doses of oral SU at 25, 37.5, or 50 mg for 2 wks during 3-wk cycles (Schedule 2/1) or for continuous 3 wk cycles (CDD schedule) with C (AUC=6 mg^{*}min/mL) plus P (175–200 mg/m²) every 21 days. Adverse events (AEs) were evaluated for dose limiting toxicities (DLTs) to determine the maximum tolerated dose (MTD) of SU plus C/P.

As of Feb 2008, a total of 28 pts were enrolled in both schedules. Tumor types included pancreatic (n=5), mesothelioma, melanoma, NSCLC (each n=3), and SCLC (n=2); 50% of pts had received multiple prior systemic treatments. Three (Schedule 2/1) and one (CDD schedule) DLTs were reported:

Dose Level	n	Reported DLTs
Schedule 2/1 (C/P 175 mg/m ²)*		
SU 25 mg	9	G4 ischemic optic neuropathy
SU 37.5 mg	7	G5 GI hemorrhage G3 neutropenic infection
CDD schedule (C/P 175 mg/m ²)		
SU 25 mg	3	None
SU 37.5 mg	5	None
SU 50 mg**	2	G4 thrombocytopenia
CDD schedule (C/P 200 mg/m ²)		
SU 25 mg	2	None

*5 pts on Schedule 2/1 were not evaluable for DLTs due to early discontinuation.

**Due to myelosuppression observed in this cohort, 3 additional pts were enrolled in the previous cohort (SU 37.5 mg). G3/4 hematologic abnormalities (all pts) included neutropenia (n=19), lymphopenia (n=17) and thrombocytopenia (n=10). Other Grade 3/4 AEs included fatigue/asthenia (n=4), febrile neutropenia, dyspnea, ataxia, hypoxia, thrombosis, ulcerative esophagitis, and syncope (each n=1). Of the pts evaluable for response (n=24), 1 pt with SCLC had a confirmed PR and 1 pt with ovarian cancer had an unconfirmed PR.

In conclusion, these data suggest the dose levels tested to date are tolerable in pts with advanced STs and may represent a clinically useful treatment option. The MTD, safety, and efficacy of SU plus C/P are under further investigation.

471P PHASE I, DOSE-FINDING STUDY OF SUNITINIB (SU) IN COMBINATION WITH IRINOTECAN (IR) IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background: SU is a multitargeted oral TKI of VEGFR, PDGFR, KIT, FLT3, CSF-1R, and RET, and approved for treatment of advanced RCC and imatinib-resistant/intolerant GIST. Because SU has shown additive effects in combination with IR in human tumour xenografts, SU + IR might be of use in the clinic. This study

investigated the safety, pharmacokinetics (PK) and efficacy of SU + IR in patients with advanced solid tumours.

Methods: Cohort 1 received IR 250 mg/m² (day 1) with SU 37.5 mg/day (day 1–15) in a 3-week cycle. The primary endpoint was maximum tolerated dose (MTD). Adverse events (AEs), PK and response rate (RR) were also assessed.

Results: Twenty-one patients have been enrolled on 2 SU dosing schedules (10 at 25 mg and 11 at 37.5 mg). Mean age was 50 (32–67). Cohort 1 had 2 patients with grade (G) 4 neutropenia and G3 fatigue judged as dose-limiting toxicities (DLTs); this exceeded the MTD and dosing de-escalated to SU 25 mg/IR 250 mg/m² (cohort 2). No DLTs were observed in patients in cohort 2, although IR dose reductions did occur. Six additional patients were treated with SU 37.5 mg/IR 250 mg/m², but 2 patients had DLTs of G4 neutropenia. In cohort 1 (n = 11), G ≥3 all-causality AEs were haematologic: neutropenia (6), leucopenia (4), and sepsis (1). In cohort 2, AEs were predominantly ≤G3 non-haematologic (nausea, vomiting, asthenia) with only 1 G4 asthenia, and 2 G4 neutropenia. PK showed no clinically significant drug–drug interactions. The table shows preliminary RR (investigator assessed).

Sunitinib	Sunitinib 25 mg/day (n=10)	Sunitinib 37.5 mg/day (n=7)
Confirmed partial response	0	2
Stable disease	2	2
Progressive disease	4	2

Conclusions: SU 25 mg/day (day 1–15) with IR 250 mg/m² (day 1) in a 3-week cycle was the MTD. This combination had a manageable safety profile. Two patients with relapsed NSCLC and submandibular cancer achieved a partial response. A study with SU/FOLFIRI is ongoing in metastatic CRC patients.

472P PHASE I STUDY OF AXITINIB (AG-013736) IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS (PTS) WITH ADVANCED SOLID TUMOURS

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Background: Axitinib is an oral, potent and selective inhibitor of vascular endothelial growth factor receptors 1, 2, 3. Anti-VEGF therapies in combination with chemotherapy have been shown to improve survival in pts with advanced cancers. The aim of this multicentre study was to assess axitinib in combination with common chemotherapy regimens in pts with advanced solid tumours.

Methods: Pts received axitinib 5 mg in combination with paclitaxel/carboplatin (cohorts 1–3: P, 200 mg/m²; 3-hour infusion/C, AUC 6 mg*min/mL; 30-minute infusion), P (cohort 4: 90 mg/m² weekly), docetaxel (cohort 5: DOC, 100 mg/m² every 3 weeks), capecitabine (cohorts 6 and 7: CAP, 1000 and 1250 mg/m² BID) or gemcitabine/cisplatin (cohort 8: GEM, 1250 mg/m² on days 1 and 8/Cis, 80 mg/m² on day 1, in 3-week cycles). Plasma pharmacokinetics (PK), dose-limiting toxicity (DLT), adverse events (AEs) and objective response rate (ORR) were evaluated.

Results: Axitinib PK profiles were similar in the presence or absence of chemotherapies. DLTs, irrespective of cohort, included febrile neutropenia (n=1), neutropenia (n=1), fatigue (n=7), hypertension (n=3), hand–foot syndrome (n=2) and 1 each of infection, hyperbilirubinaemia, diarrhoea, seizure, mucositis, thrombocytopenia, nausea, anorexia and neuropathy. Objective responses by primary tumour were: gynaecological, n=5; melanoma, n=4; breast, n=3; lung, thyroid, gastrointestinal, n=2 each; and other, n=4. The table shows the number of pts with DLTs (cycle 1, grade 3 AEs) and ORR in each cohort.

Conclusions: Axitinib 5 mg BID can be combined safely with common chemotherapy regimens at standard doses with no overlapping toxicities or evidence for drug–drug interactions. Evidence of antitumour activity was observed.

	1–3 N=15	4 N=8	5 N=7	6 & 7 N=32	8 N=22
Patients with DLTs, n	4	1	2	9	3
ORR, n (%)	8 (53)	3 (38)	3 (43)	4 (13)	4 (18)

473P AXITINIB (AG-013736; AG) IN COMBINATION WITH CHEMOTHERAPY (CT): A PHASE I STUDY IN PATIENTS (PTS) WITH GASTROINTESTINAL TUMOURS

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Background: AG is an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, 3. Inhibition of VEGF improves survival in pts with metastatic colorectal cancer (mCRC) when combined with CT. The safety, pharmacokinetics (PK) and efficacy of AG plus FOLFIRI or FOLFOX was assessed in pts with gastrointestinal (GI) tumours.

Methods: In the phase I portion of the study, pts with previously treated GI tumours received leucovorin 400 mg/m², 5-fluorouracil (5-FU) 400 mg/m² bolus then 2,400 mg/m² by 46–48-h infusion, following irinotecan 180 mg/m² (FOLFIRI) or oxaliplatin 85 mg/m² (FOLFOX) plus AG starting dose of 5 mg orally BID. FOLFOX or FOLFIRI was administered once every 2 weeks. Pts were evaluated for potential PK interactions between FOLFIRI or FOLFOX and AG, adverse events (AEs) and tumour response rate.

Results: Eight pts have been enrolled into the FOLFIRI group (median age 65 years) and six pts into the FOLFOX group (median age 67 years). PK parameters for irinotecan (n=7) were similar in the presence and absence of AG: mean (% coefficient of variation [CV]) AUC_{inf} of 12,351 ng-h/mL (32) and 15,019 ng-h/mL (39), respectively. PK parameters for platinum in ultrafiltrate from oxaliplatin (n=4) were similar in the presence and absence of AG: mean (%CV) AUC_{inf} of 5,875 ng-h/mL (57) and 4,958 ng-h/mL (15), respectively. AG PK parameters were similar in the presence or absence of FOLFIRI or FOLFOX. The most common all-causality grade 3/4 AEs with FOLFIRI were neutropenia (n=3) and fatigue (n=2), and with FOLFOX were diarrhoea (n=2) and dehydration (n=2). Partial responses were achieved by 1 (13%) and 2 (33%) pts in these cohorts, respectively, and stable disease by 2 (25%) and 1 (17%) pts, respectively.

Conclusions: No PK changes were observed for the combination of AG 5 mg BID and FOLFIRI or FOLFOX. AG 5 mg BID starting dose in combination with FOLFIRI and FOLFOX was tolerable in pts with previously treated mCRC; AG therapy can be combined with either FOLFIRI or FOLFOX to optimise pt outcome. Enrolment into a randomised, 3-arm, phase II study comparing AG plus FOLFOX ± bevacizumab (Bev) with Bev/FOLFOX is ongoing to confirm the safety and antitumour activity of AG in combination with CT.

474P A PHASE I STUDY OF DAILY BIBW 2992, AN IRREVERSIBLE EGFR/HER2 DUAL KINASE INHIBITOR, IN COMBINATION WITH WEEKLY PACLITAXEL

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Objective: BIBW 2992 (TovokTM) is an oral, potent and irreversible inhibitor of both EGFR and HER2 receptor tyrosine kinases. The efficacy of cytotoxic agents can be enhanced by erBB inhibition. The primary objective of this phase I open-label dose-escalation trial was to determine the maximum tolerated dose (MTD) of BIBW 2992 in combination with weekly paclitaxel (P).

Methods: This study evaluated safety, pharmacokinetics, and anti-tumour efficacy of daily BIBW 2992 combined with P administered on days 1, 8 and 15 of a 4-weekly cycle. The dose of P was 80mg/m², and the BIBW 2992 starting dose was 20mg, escalated in successive cohorts to 40 then 50mg. After a maximum of 6 cycles of combination therapy, patients benefiting and tolerating treatment were eligible to continue single agent BIBW 2992.

Results: 13 patients with advanced solid tumours expressing erbB receptors and suitable for treatment with a taxane have been enrolled (5M/8F; median age: 58 [range: 38-69]; ECOG PS 0/1: 3/10). Two dose-limiting toxicities of fatigue and mucositis occurred at a BIBW 2992 dose of 50mg. The most frequent toxicities were fatigue, rash, mucositis and diarrhoea. Two patients with non-small cell lung cancer (NSCLC) have had an unconfirmed partial response. Maintained stable disease was seen in 7 patients (5 with NSCLC) for >4 cycles.

Conclusion: A BIBW 2992 dose of 40mg daily in combination with weekly P 80mg/m² is currently being explored as the likely recommended dose for phase II study. Promising anti-tumour activity was seen with this combination. The addition of bevacizumab to BIBW 2992 with 80mg/m² weekly P will now be evaluated. Toxicities of BIBW 2992 combined with P were generally mild to moderate and manageable.

475P A PHASE I DOSE ESCALATION TRIAL OF BIBW 2992, AN IRREVERSIBLE EGFR/HER2 KINASE INHIBITOR, FOR 20 AND 13 DAYS IN COMBINATION WITH DOCETAXEL EVERY 21 DAYS

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Objectives: The primary objective of this Phase I open-label dose-escalation study was to determine the maximum tolerated dose (MTD) of BIBW 2992 (Tovok™), an oral irreversible inhibitor of epidermal growth factor receptor (EGFR)/human epithelial receptor 2 (HER2) tyrosine kinase, in combination with docetaxel on two application schedules (20 and 13 days of continuous BIBW 2992) in patients with advanced solid tumours. Secondary endpoints included pharmacokinetics (PK), overall safety and efficacy.

Methods: Thirty-one patients with advanced, non-resectable and/or metastatic solid tumours, who failed prior standard therapies and whose tumours were classically known to express EGFR/HER2 were enrolled. BIBW 2992 was administered on days 2-21, or 2-14, with docetaxel (60 or 75 mg/m²) administered on Day 1 of each 21-day cycle. After an initial dose of docetaxel 60 mg/m² and 75 mg/m², BIBW 2992 was escalated by 10 mg increments until the MTD was determined. PK sampling was performed on days 2, 3 and 10 of treatment cycles 1 and 2.

Results: The MTD determined for 75 mg/m² docetaxel i.v. in combination with oral BIBW 2992 on the 20-day schedule was 20 mg qd. The most frequent adverse events at all study drug doses consisted of gastrointestinal (96.8%) and haematological (93.5%) toxicities. No dose escalation of BIBW 2992 beyond 20 mg was possible in both schedules tested. No apparent drug-drug interaction between BIBW 2992 and docetaxel was observed. Stable disease was seen in 14 (45%) of patients treated with docetaxel and BIBW 2992.

Conclusions: The MTD for the combination of BIBW 2992 for 20 days plus docetaxel 75 mg/m² was 20 mg BIBW 2992 qd. The MTD was not determined for the 13-day BIBW 2992 schedule. No complete or partial responses were seen.

476P PHASE 1 COMPARISON OF PHARMACOKINETICS, SAFETY AND EFFICACY WITH LOW VERSUS HIGH DOSES OF ABT-869 IN REFRACTORY SOLID TUMORS

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Background: ABT-869 is an orally bioavailable, potent and specific inhibitor of all vascular endothelial growth factor and platelet derived growth factor family receptor tyrosine kinases (RTKs). In preclinical tumor growth studies, ABT-869 exhibited efficacy in human fibrosarcoma, breast, colon, and small-cell lung carcinoma xenograft models.

Methods: In study M04-710 conducted in refractory solid tumor patients in Singapore, ABT-869 was orally administered once daily at bedtime under fasting conditions in 21-day cycles. As a portion of this study, the pharmacokinetics (PK), safety and efficacy were evaluated in patients treated with 0.10 mg/kg (11 patients) versus 0.25 mg/kg (12 patients).

Results: 33 patients enrolled in study M04-710 at treatment doses ranging between 0.10 and 0.30 mg/kg. The time to maximum plasma concentration was 3.5 ± 1.5 h or 2.7 ± 0.8 h for the 0.10 and 0.25 mg/kg doses, respectively. Similarly, the elimination half-life was 19.0 ± 5.6 versus 18.9 ± 6.2 h. The clearance and dose normalized steady-state exposures were also similar between 0.10 and 0.25 mg/kg doses (2.3 ± 0.9 and 0.35 ± 0.15 vs. 3.0 ± 1.3 L/h and 0.30 ± 0.08 µg*hr/mL/mg, respectively). The PK appeared dose-proportional between 0.10 mg/kg and 0.30 mg/kg and time-invariant after repeated dosing from day 1 to 15. 2 incidences of grade 3 proteinuria and 1 of grade 3 hypertension were observed at the 0.10 mg/kg dose. At the 0.25 mg/kg dose, there was 1 incidence of grade 3 proteinuria, 1 of grade 4 proteinuria and 1 of grade 3 hypertension. Overall, in study M04-710, 17 patients (51%) experienced stable disease for ≥ 3 months and 3 patients experienced a partial response, 2 with non-small cell lung cancer (NSCLC) and 1 with colorectal cancer. The 0.10 and 0.25 mg/kg doses are currently being evaluated in a randomized phase 2 NSCLC study.

Conclusion: ABT-869 is a novel RTK inhibitor with pharmacokinetics that are dose-proportional over the 0.10-0.30 mg/kg dose range and time-invariant after repeated dosing, an acceptable safety profile and an early demonstration of anti-tumor activity. Efficacy will be further investigated in phase 2 trials.

477P PRELIMINARY ANALYSIS OF ABT-869 SAFETY, PHARMACOKINETICS AND EFFICACY IN THREE PHASE 2 SOLID TUMOR STUDIES

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Background: ABT-869 is an orally bioavailable, potent and specific inhibitor of all vascular endothelial growth factor and platelet derived growth factor family receptor tyrosine kinases (RTKs). The pharmacokinetics (PK) appeared dose-proportional between 0.10 mg/kg and 0.30 mg/kg and time-invariant after repeated dosing from Day 1 to 15. The elimination half-life ranges from 13.9 to 23.1 h. In a phase 1 study of patients (N=27) with refractory solid malignancies the following grade 3/4 adverse events were observed: 4 patients with fatigue, 4 with hypertension, 4 with proteinuria and 1 with a skin related event. Broad anti-tumor activity was observed.

Methods: 3 phase 2 monotherapy studies are being conducted internationally to determine the efficacy and to establish the safety/tolerability profile of ABT-869. ABT-869 was orally administered daily at bedtime, with no food or beverage 2-h before and after ABT-869 dose in a 21-day cycle. Child-Pugh A (CP-A) patients, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) patients were treated once daily and Child-Pugh B (C-PB) patients were treated every other day. Patients were treated at 0.25 mg/kg, although the NSCLC study also had a 0.10 mg/kg study arm.

Results: A total of 78 patients enrolled in the three studies: 42 patients with relapsed or refractory NSCLC (M06-880), 18 patients with sunitinib refractory RCC (M06-882) and 18 patients with advanced HCC, 16 C-PA and 2 CP-B (M06-879). In study M06-882 there was 1 incidence of grade 3 hypertension, 1 incidence of grade 3 fatigue and 1 incidence of grade 2 proteinuria while in study M06-879, 2 incidences of Grade 3 hypertension and 2 incidences of Grade 2 proteinuria were observed. In these studies, 4 NSCLC patients, 2 RCC patients and 2 HCC patients, active ≥ 16 weeks experienced stable disease. In addition, in study M06-879, some patients exhibited a downward trend in alpha-fetoprotein. All available preliminary PK data from the 3 studies will be reported in the poster.

Conclusion: ABT-869 is a novel RTK inhibitor with an acceptable safety profile and anti-tumor activity against a range of solid malignancies.

478P PHARMACOKINETICS OF BIBF 1120 AFTER ADMINISTRATION OF SINGLE DOSES OF 100 MG [14C]-BIBF 1120

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Objectives: BIBF 1120 is a novel, potent and orally available tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1/2/3, platelet-derived growth factor receptor (PDGFR) α/β and fibroblast growth factor receptor (FGFR) 1/3 which showed encouraging efficacy signals in a Phase II

trial in advanced non-small-cell lung cancer (NSCLC) patients. The primary objective of this Phase I study was to investigate the pharmacokinetics and the mass balance of a single oral dose of [¹⁴C]-radiolabelled BIBF 1120.

Methods: Eight healthy male volunteers were exposed to a single dose of 100 mg [¹⁴C]-radiolabelled BIBF 1120 drinking solution. Blood-, urine- and faeces samples were collected over a period of 120 h after drug intake. Plasma- and urine BIBF 1120 concentrations were analysed using high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry. [¹⁴C]-radioactivity levels in plasma, whole blood, urine and faeces were analysed by liquid scintillation counting methods.

Results: [¹⁴C]-radiolabelled BIBF 1120 was rapidly absorbed. Mean C_{max} values occurred 1.3 hours after oral administration. A high gMean apparent total body clearance (CL/F) of 16300 mL/min was observed. In addition, BIBF 1120 exhibited a high gMean apparent volume of distribution (V_z/F). The sum of [¹⁴C] radioactivity of BIBF 1120 and its main metabolite BIBF 1202 was significantly lower than the total [¹⁴C] radioactivity in plasma. [¹⁴C]-radiolabelled BIBF 1120 was mainly eliminated via the liver with a faecal excretion rate of 93.4% within 120 hours after dosing. The contribution of renal excretion to the total clearance was 0.65% of the total [¹⁴C] radioactivity. The overall recovery was complete (>90%) already 4 days after dosing. BIBF 1120 was well tolerated with only mild adverse events of short duration.

Conclusions: BIBF 1120 was mainly excreted via the faeces. The data suggest the presence of one or more BIBF 1120 metabolites besides BIBF 1202. BIBF 1120 was safe and well tolerated at a single dose of 100 mg.

479P

PHASE I STUDY OF CEDIRANIB, A VEGFR SIGNALING INHIBITOR, IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

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Background: Cediranib (RECENTINTM, AZD2171) is an oral, highly potent and selective inhibitor of vascular endothelial growth factor (VEGF) signaling, with activity against VEGFR-1, -2 and -3.

Methods: In part A (dose-ascending phase), patients (pts) with advanced solid tumors refractory to standard therapies received a single oral dose of cediranib 10–45 mg and, following a 6–8-day washout period, continued once-daily treatment at the same initial dose. If ≥50% pts in a dose cohort developed dose-limiting toxicities (DLTs), the dose one level below was determined to be the maximum tolerated dose (MTD). In part B (expanded-cohort phase), pts with non-small-cell lung cancer (NSCLC) and colorectal cancer (CRC) received cediranib at the MTD.

Results: In part A, 16 pts with NSCLC (5), CRC (4) or other tumor types (7) received cediranib 10 (3), 20 (3), 30 (3) or 45 (7) mg/day. Cediranib 30 mg/day was defined as the MTD for further investigation in part B, since 3/6 evaluable pts receiving ≥45 mg/day experienced 4 DLTs (proteinuria, n=2; diarrhea, n=1; thrombocytopenia, n=1). Following a single dose of cediranib 10–45 mg, the maximum plasma concentration was achieved 2–3 hours post dosing and the mean terminal half-life ranged from 19–28 hours. At 20 mg/day, the unbound minimum plasma concentration was 3.8 times the human umbilical vein endothelial cell proliferation IC₅₀. In part B, 24 pts with NSCLC or CRC (12 each) received cediranib 30 mg/day. The overall adverse event profile and PK parameters were similar to those seen in a Western population. The most common (≥60%) adverse events and laboratory abnormalities of any grade were diarrhea (85%), hypertension (80%), hand-foot syndrome (68%), fatigue (65%), blood erythropoietin increased (73%), blood TSH increased (70%), and proteinuria (68%). Upward tendency in VEGF and reductions in soluble VEGFR-2 were observed in part B. There were two partial responses (alveolar soft tissue sarcoma in part A; CRC in part B) and 24 pts with stable disease ≥6 weeks (8 in part A; 16 in part B). Six pts in part A have continued with cediranib for >1 year.

Conclusions: Cediranib ≤30 mg/day was generally well tolerated and showed encouraging antitumor activity.

480P

A PHASE I DOSE ESCALATION STUDY OF SUNITINIB (SU) IN COMBINATION WITH PEMETREXED (PEM) IN PATIENTS (PTS) WITH ADVANCED SOLID MALIGNANCIES

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SU is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R and RET, approved multinationally for the treatment of advanced RCC and imatinib-resistant/intolerant GIST. SU enhanced the antitumor activity of Pem in NSCLC xenograft studies. In this ongoing phase I study of advanced solid malignancies, successive pt cohorts received oral SU at 25, 37.5 or 50 mg as a 3-wk continuous daily dose (CDD schedule) or as a 2-wk daily dose followed by 1 week of rest in a 3-wk cycle (Schedule 2/1) with escalating doses of Pem at 300–500 mg/m² IV q21d. Safety, maximum-tolerated doses (MTD), highest dose at which 0/3 or ≤1/6 pts had a dose-limiting toxicity [DLT; predefined treatment-related G3/4 AE during Cycle 1], pharmacokinetic (PK) profiles and objective response (RECIST) were evaluated. As of March 2008 (study is ongoing), 20 pts (NSCLC n=3) received SU (CDD schedule) + Pem in 4 dose-escalation cohorts and 7 pts (NSCLC n=1) received SU on Schedule 2/1 (SU 50 mg + Pem 500 mg/m²); the 27 pts received >103 cycles of therapy in total. For the CDD cohorts, DLTs were G3 febrile neutropenia (SU 37.5 mg + 500 mg/m² Pem; n=1), G3 anorexia ≥7 days, and G5 cerebral hemorrhage (SU 50 mg + 500 mg/m² Pem; each n=1). MTD was established as SU 37.5 mg + Pem 500 mg/m². In Schedule 2/1, 1 pt experienced a DLT, febrile neutropenia, occurring at the MTD: SU 50 mg + Pem 500 mg/m². On Schedule 2/1 there were no SU-related non-hematologic G4 AEs (G3: fatigue, nausea, anorexia, vomiting, dehydration, each n=1). G3/4 hematologic abnormalities at the MTDs of both schedules will be presented. PK data (C_{max}, AUC) revealed no clinically significant drug–drug interactions. On the CDD schedule, 2 pts (bile duct cancer: SU 37.5 mg + Pem 300 mg/m²; NSCLC: SU 50 mg + Pem 500 mg/m²) had partial responses and 8 pts had stable disease (≥8 weeks) across the 4 dose-escalation cohorts; 2 pts for >6 months. Data from an expansion cohort of NSCLC pts will be presented. In summary, SU 37.5 mg/day (CDD schedule) and SU 50 mg/day (Schedule 2/1) both with Pem 500 mg/m² q21d have manageable safety profiles and show preliminary evidence of antitumor activity. The CDD regimen is undergoing further study in NSCLC pts.

481P

SAFETY AND PHARMACOKINETICS (PK) OF MOTESANIB DIPHOSPHATE IN COMBINATION WITH GEMCITABINE AND ERLOTINIB FOR THE TREATMENT OF SOLID TUMORS

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Objectives: Motesanib is an oral, investigational, highly selective inhibitor of VEGF, PDGF and Kit receptors. This ongoing, open-label, dose-finding, phase 1b study establishes the maximum-tolerated dose (MTD) of motesanib when combined with gemcitabine (G) and the EGFR inhibitor erlotinib (E). The safety of motesanib, the PK of these agents, and antitumor activities are evaluated.

Methods: Patients (pts) have documented solid tumors, ECOG 0–2 and no prior G, E or anti-VEGF therapy. Control (ctrl) receives G (1000mg/m² IV QW for 7/8 wks, cycle 1; then 3/4 wks, cycle 2+) and E (100mg QD) from day 1; cohorts (C) 1, 2, 3, and 4 receive G and E plus escalating doses of motesanib continuously from day 9, cycle 1; C5 and C6 receive E (150mg QD) plus motesanib (see Table). Dose-limiting toxicities (DLTs) are defined as any treatment-related hematologic or nonhematologic gr 3 or 4 toxicities (except alopecia) through wk 5.

Results: 57 pts (59% female, 91% disease stage IV) are enrolled (C1/2/3/4/5/6/ctrl, n=7/9/9/10/7/7/8), with 48 pts receiving ≥1 dose of motesanib. Dose escalation and DLTs are shown in the Table. The MTD for motesanib in C1–4 was 100mg QD. 40 pts had motesanib-related adverse events (AEs): gr 3/4, n=12/4 in C1–4; n=7/0 in C5–6. Related AEs of interest include gr 3 deep vein thrombosis (n=2, C3), congestive cardiac failure (n=1, C2), neutropenia (n=1, C4), and cholecystitis (n=1, C3); and gr 4 febrile neutropenia (n=1, C1), neutropenia (n=1, C4), and pulmonary embolism (n=2, C3). G/E coadministration did not markedly change median motesanib PK parameter values at 50–125mg QD; E exposures were 25%–40% (C_{max}) and 10%–60% (AUC) lower with motesanib. There is 1 confirmed PR in C4 (non-small cell lung cancer) and 22 SD (C1–4/5/ctrl, n=15/2/5).

Conclusions: Combining motesanib with G and E was tolerable. The PK of motesanib was not affected, while exposure for E appeared to be lower. Updated data will be presented. Summary of DLTs.

Motesanib Dose Cohort	DLTs
Cohort 1, n=7: G/E+50mg QD	n=1: gr 4 febrile neutropenia
Cohort 2, n=8: G/E+100mg QD	n=0
Cohort 3, n=9: G/E+125mg QD	n=3: gr 3 cholecystitis; vomiting/nausea; nausea/jaundice/subdural hematoma/cognitive disorder
Cohort 4, n=10: G/E+75mg BID	n=3: gr 3 neutropenia; nausea; tumor necrosis
Cohort 5, n=7: E (150mg QD)+100mg QD*	n=0
Cohort 6, n=7: E (150mg QD)+125mg QD	n=2: gr 3 fatigue; rash

*MTD established in cohorts 1-4

482P NITRIC OXIDE SYNTHASE (NOS) INHIBITION IN CANCER PATIENTS: CARDIOVASCULAR EFFECTS AND RELATIONSHIP TO PHARMACOKINETIC (PK) AND TUMOUR BLOOD VOLUME (BV) MEASUREMENTS

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Aim: NOS inhibition was recently shown to have tumour anti-vascular activity in cancer patients. However, its potential cardiovascular toxicity might limit its use in the clinic. We present additional analyses of the cardiovascular changes observed after patients received the NOS inhibitor N-nitro L-arginine (L-NNA), and its effects on PK measurements and tumour BV changes.

Patients and methods: 18 patients with histologically confirmed cancer were enrolled prospectively into a phase 1 dose escalation study of L-NNA. Patients with hypertension or cardiac medical conditions were excluded. All patients received a single intravenous dose of L-NNA. Blood pressure (BP) monitoring was performed every five minutes for the first hour, and hourly for 6 hours after L-NNA. Plasma samples were taken from all patients for PK analysis using high-performance liquid chromatography with absorbance detection. Tumour BV measurements were obtained from the final 8 patients using dynamic contrast enhanced computed tomography.

Results: After L-NNA, mean systolic and diastolic BP increased by 6.2% (p<0.001) and 10.5% (p<0.001) respectively, returning to baseline by 3 hours. Reductions in tumour BV were observed at 1 hour (42.9%, p=0.007), sustained to 24 hours (33.9% p=0.035), and correlated with L-NNA plasma area under the curve (AUC) (r=0.83, p=0.010). There was no significant correlation between L-NNA plasma AUC and changes in systolic (r=0.09, p=0.73) or diastolic BP (r=0.01, p=0.97). There was no significant correlation between tumour BV changes at 1 hour and changes in systolic (r=0.63, p=0.09) or diastolic BP (r=0.15, p=0.72), and between tumour BV changes at 24 hours and changes in systolic (r=0.14, p=0.74) or diastolic BP (r=0.13, p=0.76).

Conclusion: NOS inhibition causes transient hypertension, postulated to occur through a change in vascular resistance. Increases in BP after L-NNA do not correlate with the degree of tumour blood volume reduction, or with L-NNA plasma AUC, whereas dose-dependent reductions in tumour BV were observed. Nitric oxide is a potential target for anti-vascular cancer treatment.

483P PHASE IB STUDY TO DEFINE THE OPTIMAL LOW DOSE OF NGR-HTNF, A NOVEL VASCULAR TARGETING AGENT (VTA), IN COMBINATION WITH CISPLATIN IN PATIENTS (PTS) WITH SOLID TUMOURS

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Background: NGR-hTNF is a VTA exploiting a tumour-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumour blood vessels. At low doses, NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity. Consistently, preclinical data indicate significant synergy between low doses of NGR-hTNF and cisplatin.

Methods: Pts with refractory solid tumours were treated with low doses (20-200 fold lower than MTD) of NGR-hTNF given with a doubling-dose scheme (0.2-0.4-0.8-1.6 µg/m²) as 1-hour intravenous infusion, in combination with cisplatin 80 mg/m²,

both given every 3 weeks. A 3+3 escalation/de-escalation design was followed. Blood samples for PK analysis were collected after the first 3 cycles. Definition of DLT: any severe (G3-4) toxicity clearly related to NGR-hTNF.

Results: 19 pts (median age: 59 years [range, 47-73]; 13M/6F; ECOG PS 0/1 10/9) were enrolled. Tumour types were: colorectal (6 pts), NSCLC (5), mesothelioma (4), sarcoma (2), and melanoma (2). Median number of prior regimens was 3 (range, 1-6), with 9 and 6 pts pre-treated with platinum- and oxaliplatin-based regimens, respectively. Both NGR-hTNF C_{max} and AUC increased linearly with dose. The combination was safe without PK interaction or exacerbation of platinum-associated toxicity profile. As expected for the low doses explored, MTD was not reached and no DLTs were registered at 0.2 µg/m² (n=4), 0.4 µg/m² (n=3) and 1.6 µg/m² (n=3). At 0.8 µg/m² (n=8), a pt experienced a G3 transient acute infusion reaction, not surely dose-related. Nevertheless, this cohort was expanded up to 6 pts for safety reasons, with no DLTs registered, and subsequently up to 12 pts, for preliminary anti-tumour activity evaluation. At this DL, two NSCLC pts, with documented PD after platinum-based regimens, achieved a confirmed PR and a significant tumour shrinkage (-28%), and two pts with rectal cancer and sarcoma had SD lasting 20+ and 12+ weeks, respectively.

Conclusion: The combination of NGR-hTNF 0.8 µg/m² with cisplatin 80 mg/m² shows a manageable toxicity profile and promising preliminary antitumor activity and will be further developed.

484P A PHASE 1 STUDY OF MP470, A NOVEL ORALLY BIOAVAILABLE SMALL MOLECULE WITH RAD 51 SUPPRESSION ACTIVITY

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Introduction: MP470 is a novel orally bioavailable small molecule with inhibitory activity against several protein tyrosine kinase targets including mutant c-Kit, mutant PDGFR α , mutant FLT3. MP470 also sensitizes cancer cells to platinum-based DNA damaging agents and to XRT, presumably through the suppression of Rad51, a key component to the cellular repair machinery in response to DNA double-strand breaks.

Methods: Adult pts with unresectable or metastatic solid tumors refractory to standard therapies or for which no standard therapy exists, and KPS \geq 70 were eligible. The study followed an Accelerated Titration Design with 1 pt/cohort until DLT is observed at one dose level or G2 MP470-related AEs at two dose levels, then 3 pts/cohort until MTD is reached. Dose escalation based on the modified Fibonacci sequence. Intra-patient dose escalation is permitted beginning with Cycle 2. Objectives are to evaluate safety and tolerability, determine MTD, estimate therapeutic response rate (RECIST), PK profile, and PK-PD relationship. PD assessments include Rad51 (Targeted Molecular Diagnostics [Westmont, IL]) in skin.

Results: Ten pts (26-80 yrs; 6M/4F) received 100-900 mg/d MP470 for median of two 28-day cycles (range, 1-4). No DLTs were observed. Three pts (30%) with G2 or G3 AEs: G2 leukopenia on D4 (500 mg/d); G3 anxiety on D26 (700 mg/d); G3 AST elevation on D15 (700 mg/d). No additional significant toxicity has occurred. Favorable PK was observed. Rad51 modulation occurred with MP470 administration. A positive FDG-PET response was observed on D15 in a G1ST pt (900 mg) who previously failed imatinib and sunitinib therapies. Notably, the percent change in SUVmax from BL in the pelvis, retrocrural and left lower lobe was reported at 32% (21.3 vs. 14.5), 32% (10.5 vs. 7.1), and 14% (7.8 vs. 6.7), respectively. Dose escalation will continue until the MTD is reached.

Conclusions: MP470 is bioavailable and daily dosing appears safe and tolerable at doses up to 900 mg with Rad51 modulation. These results strengthen the rationale for combining MP470 with DNA-damaging agents due to the ability of MP470 to suppress the Rad51 DNA repair mechanism. A phase-1b trial of MP470 in combination with standard chemotherapies has been initiated.

485P FIRST RESULTS FROM A PHASE 1B STUDY OF THE ANTI-EPCAM ANTIBODY ADECATUMUMAB (MT201) IN COMBINATION WITH DOCETAXEL IN PATIENTS WITH METASTATIC BREAST CANCER

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Background: Overexpression of the epithelial cell adhesion molecule (EpCAM) has been associated with poor outcome in breast cancer. Data from a previous Phase 2 study in MBC suggested that single agent treatment with the anti-EpCAM antibody adecatumumab could overcome this negative prognostic effect and prolong progression-free survival in patients with high-level EpCAM expression.

Methods: EpCAM-positive MBC patients were treated with docetaxel (100mg/m²; q21d) in combination with adecatumumab q21d (dose levels tested: 180mg/m² and 550mg/m²). Patients were grouped into high- and low-level EpCAM expressors according to previously published methodology (Spizzo et al., 2004). Primary objectives were safety and tolerability of the combination treatment. Secondary objectives were PK and anti-tumor activity according to RECIST.

Results: A total of 19 patients with a median of 3 prior chemotherapy lines (95% pretreated with anthracyclines and 68% with taxanes) were enrolled. No evidence for aggravation of grade 3/4 toxicities typically associated with docetaxel treatment was found. At 550mg/m², 3 of 11 patients experienced grade 3 diarrhea (2 patients for < 24 hours). Other frequently observed adverse events of any grade comprised nausea, vomiting, stomatitis, constipation, fatigue, fever, chills, mucosal inflammation, alopecia, anorexia, enzyme abnormality, headache, cough, dyspnoea, and hot flushes. The overall response rate (CR/PR) in all evaluable patients was 20%. Patients with high EpCAM expression showed a response rate of 43%, whereas no responses were detected in patients with low EpCAM expression on the tumor.

Conclusions: These results demonstrate that combining adecatumumab with docetaxel is overall safe and feasible. Diarrhea appears to be the main toxicity at higher doses but is clinically well manageable in most cases. The response rate observed in this heavily pre-treated population is encouraging and the difference in outcome depending on EpCAM expression levels is in line with earlier observations. Further development of adecatumumab combinations in patients with tumors expressing high levels of EpCAM is warranted.

486P **A PHASE I STUDY OF CS055, A NOVEL HISTONE DEACETYLASE INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMORS AND LYMPHOMAS**

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Background: CS055 is a new benzamide type of histone deacetylase (HDAC) inhibitor with Class I HDAC selectivity. CS055 has exhibited significant broad-spectrum in vivo anti-tumor activity, and an attractive safety profile in preclinical development. This Phase I study is to evaluate safety and tolerability of CS055 in patients (pts) with advanced solid tumors and lymphomas.

Methods: Pts with refractory or relapsed advanced solid tumors and lymphomas were enrolled in this study. CS055 was administered orally twice per week for 4 consecutive weeks, with 2-week recovery period between cycles. Patients with SD or better were eligible to continue therapy.

Results: To date, 22 pts (15M/7F, median age 49 yrs) have been treated with 6 dose levels (flat dosing with 5, 10, 17.5, 25, 32.5 and 50mg). All 22 pts were evaluated for safety, and no dose limiting toxicities have been identified. The most common treatment related toxicities were grade 1 and 2, including fatigue 45%, anorexia 23%, dizziness 23%, nausea 18%, diarrhea 18%, fever 14%, flatulence 14%, thrombocytopenia 14%, leucopenia 14%, anemia 9% and neutropenia 4.5%. No prolonged QTc interval was observed. 21 pts (6 lymphomas, 15 solid tumors with various types) with total treatment cycles of 40 (range 1-6) were evaluable for efficacy. 3 pts with lymphomas achieved PR (2 confirmed, 1 unconfirmed), and 9 pts (1 lymphoma, 8 solid tumors) experienced SD. Single dose PK analysis was performed at the dose levels of 25, 32.5 and 50 mg, each with 4 pts. The results revealed T_{1/2} of 17 h with the range of 13-24 h, T_{max} of 1-2 h in most cases, and a dose-dependent increase in C_{max} (40, 140, and 234 ng/mL for 25, 32.5, and 50 mg, respectively). To date, histone (H3) acetylation status of the whole peripheral WBC from pts treated with 25 and 32.5 mg has been analyzed by an ELISA-based assay, and significant inhibition of HDAC activity was observed, which lasted for 3 days in most pts after single dosing with CS055.

Conclusions: In general, CS055 was well-tolerated in pts with advanced solid tumors and lymphomas in the current regime. MTD has not been reached. A regime of 3x/week for 4 consecutive weeks is currently ongoing to evaluate tolerance, potential efficacy and multi-dosing PK/PD parameters.

487P **PANOBINOSTAT (LBH589) PHARMACOKINETICS (PK): IMPLICATION FOR CLINICAL SAFETY AND EFFICACY**

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Deacetylase inhibitors (DACi) are a novel class of anticancer agents that target epigenetic changes via gene expression modulation. Panobinostat (LBH589), a hydroxamic acid derivative, is a potent DACi with antitumour activity in the nanomolar range, demonstrates preclinical activity in a wide variety of mice bearing haematological and solid tumor xenografts, and shows promising clinical activity. Panobinostat concentrations in plasma were evaluated in 156 patients with solid and

haematological malignancies receiving oral panobinostat at doses of 10 - 80 mg (Days 1, 3, 5 weekly or every other week or days 1, 4 weekly) in two Phase I studies. PK was analyzed by non-compartmental methods. The relationship between Cycle 1 PK and clinical endpoints was explored. Panobinostat exhibited rapid oral absorption [median T_{max} 1 h (range, 0.5 to 3 h)] and elimination (mean effective t_{1/2} 15.6 h). Slight drug accumulation (1.4-fold) was observed. Inter-individual variability of systemic exposure was 60%. A positive linear relationship was found between panobinostat doses studied and C_{max} (Rs= 0.55; p< 0.05) or AUC (Rs= 0.36; p< 0.05), but without clear dose-proportionality. Apparent clearance did not correlate with body surface area, weight, gender, or age indicating the appropriateness of flat fixed dosing. Clinical endpoints showed a correlation with panobinostat dose but not PK. Doses ≥ 20 mg produced partial and complete responses in patients with cutaneous T-cell lymphoma, leukemia, and lymphoma (HL, NHL), while doses ≥ 40 mg were associated with an increased incidence of fatigue and grade III/IV haematologic toxicity. Panobinostat dose appears to be a better predictor of clinical safety and response than PK. The dose-clinical endpoint relationship suggests that oral doses in the range of 20 - 40 mg/d given three times weekly may provide clinical benefit and warrant phase II evaluation. Doses > 40 mg with this schedule may be possible in subsets of patients (e.g., patients with AML) in whom severe thrombocytopenia is common and treated supportively.

488P **A PHASE 1B STUDY OF AMG 655 IN COMBINATION WITH PACLITAXEL AND CARBOPLATIN IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER**

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AMG 655 is a fully human IgG1 monoclonal agonist antibody that binds human death receptor 5, activates caspases, and induces apoptosis in sensitive tumor cells. The objectives of this ongoing study are to assess the safety and pharmacokinetics (PK) of AMG 655 in combination with paclitaxel and carboplatin (PC). Eligible patients (pts) were ≥ 18 years old with untreated, advanced non-small cell lung cancer (NSCLC) and an ECOG score of 0 or 1. Pts were enrolled in sequential dose cohorts of AMG 655 (5 or 15 mg/kg) plus P (200 mg/m²) and C (AUC = 6 mg/mL x min) IV every 3 weeks for up to 6 cycles. Endpoints include incidence dose-limiting toxicities (DLTs), adverse events (AEs), PK parameters, and objective tumor response rate. As of 4/08, 12 pts had received ≥ 1 dose of AMG 655 and PC. Ten pts were men; 11 pts were ECOG 1, and the median (range) age was 68.5 (50-83) years. Median (range) time on treatment was 18.3 (1.1-30.6+) weeks; 5 pts remain on AMG 655. There was 1 DLT: grade 3 hyponatremia in 1 pt (15-mg/kg cohort). AEs are shown in the table. Following one 5-mg/kg dose of AMG 655 after chemotherapy, AMG 655 PK values (serum clearance, C_{max}, AUC) were similar to the first-in-human study (LoRusso et al. JCO 2007; 25: abstract 3534) indicating no effect of PC on PK of AMG 655. Preliminary data indicate no effect of AMG 655 on PK of P. Tumor-response data were available for 10 pts: 1 complete response, 3 partial responses, 3 with stable disease, and 3 with progressive disease. AMG 655 administered with PC appears to be well tolerated with expected PK properties not altered by PC. A phase 2 trial is ongoing. AEs in ≥ 3 pts.

Preferred Term	All AEs	CTCAE Grade 3 ^a	CTCAE Grade 4 ^a
At least 1 event - n (%)	12 (100)	7	3
Anorexia	8	0	0
Fatigue	7	0	0
Alopecia	6	0	0
Nausea	6	1	0
Arthralgia	5	1	0
Myalgia	5	1	0
Vomiting	4	0	0
Neutropenia	4	1	2
Constipation	3	0	0
Dyspnea	3	1	0
Peripheral sensory neuropathy	3	1	0

^aWorst grade. Other AEs (no. pts) with CTCAE grade 3 include abdominal pain (1), cardiac failure (1), drug hypersensitivity (1), hyponatremia (1), leucopenia (1), pyothorax (1), respiratory track infection (1), and syncope (1).

Other AEs (# pts) with CTCAE grade 4 include pulmonary embolism (1).

489P PHASE 1 STUDY OF THE NOVEL PROTEASOME INHIBITOR NPI-0052 IN PATIENTS WITH ADVANCED MALIGNANCIES INCLUDING LEUKEMIAS

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Background: NPI-0052 is a novel proteasome inhibitor that produces prolonged inhibition of all three catalytic activities of the 20S proteasome. Preclinical models suggest NPI-0052 may demonstrate an improved therapeutic ratio and activity in hematologic (myeloma, lymphoma, leukemia) and solid tumor malignancies. Phase 1 studies are being conducted in patients with myeloma, lymphomas, leukemias and solid tumors.

Materials and methods: In this study cohorts of 3 or more patients with solid tumor, lymphoma or leukemia were treated with NPI-0052 administered weekly, for 3 weeks in 4-week cycles in this 3+3 design dose escalation study. The dose of NPI-0052 was escalated in 50-100% increments dependent on observed adverse events (AE). In addition to regular safety monitoring, proteasome inhibition (PI) (baseline, D1 & D15) and PK (D1 & D15) were assayed in blood. Once a Recommended Phase 2 Dose (RP2D) is identified, an RP2D cohort of patients with CLL will be enrolled.

Preliminary results: 13 patients have been treated at doses ranging from 0.1 mg/m² to 0.3 mg/m² without reaching an MTD. The AE profile has been tolerable. Preliminary PK data indicate an T1/2 of approximately 3-4 minutes, with clearance at 15.5+/-17.6 L/min and Vz of 115+/-243 L. PI has been assayed in blood, indicating a dose:response relationship with inhibition of up to 78% observed. No responses have been confirmed, however, 4 patients have had stable disease for at least 2 cycles, including one with mantle cell lymphoma (4 months), one with Hodgkin's lymphoma (4 months), one with melanoma (4 months), and one with sarcoma (5 months).

Conclusions: NPI-0052 produces dose-dependent pharmacologic effects into the predicted effective range at doses below the MTD. Enrollment continues to identify a RP2D based on safety, efficacy and / or PD. Combination studies are being initiated in solid tumor diagnoses with other targeted agents.

490P INTEGRATED SAFETY ANALYSIS OF THE OXIDATIVE STRESS INDUCER ELESCLOMOL (FORMERLY STA-4783) CO-ADMINISTERED WITH PACLITAXEL

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Background: Elesclomol is a novel small-molecule oxidative stress inducer known to synergize with taxanes and certain other chemotherapeutics. Co-administered with paclitaxel (E+P), it demonstrated activity in metastatic melanoma in a recent randomized Phase 2 trial.

Methods: Between 2003 and 2006 at >20 sites, a total of 3 Phase 1 (solid tumors) and 2 Phase 2 (melanoma, sarcoma) clinical trials of E+P were completed. Various dose regimens were explored, and 1 randomized, blinded study had a paclitaxel control. Exposure, adverse event (AE) and lab data were combined. All AE data were graded per CTCAE v.3 and re-coded to MedDRA 9.0. All treated patients (pts) were analyzed by treatment received.

Results: 239 pts received E+P, with 224 receiving E at or above 213 mg/m², the dose currently under investigation in a Phase 3 trial in metastatic melanoma. A control group of 30 pts received P alone. Of 269 total treated pts, 62% were male, 89% were Caucasian; mean age = 57. Mean E+P treatment duration = 85 d (range 1 to 554 d). The most frequent AEs for E+P pts (N=239) were fatigue (53%), alopecia (43%), nausea (40%), constipation (23%), and diarrhea (23%). Neutropenia was the most frequent ≥Grade 3 AE, occurring in 6% of E+P pts vs. no P-alone pts. Other ≥Grade 3 AEs occurring in ≥3% of E+P pts were anemia, DVT, dyspnea, fatigue, hyperglycemia, hypophosphatemia, leukopenia, and extremity pain (3% each). With the exception of ≥Grade 3 leukopenia and extremity pain, which did not occur in P-alone pts, these other ≥Grade 3 AEs occurred in comparable % of P-alone pts (anemia, DVT, dyspnea, hyperglycemia, hypophosphatemia, 3% each; fatigue, 7%). The most frequent non-neoplastic AEs resulting in E+P discontinuation were hypersensitivity reactions (3%), nervous system disorders (2%), and respiratory disorders (2%); comparable % of P-alone pts discontinued P for these reasons (3%, 10%, and 3%, respectively).

Conclusions: Given via various dosing regimens to oncology populations, E+P appeared to be well tolerated; no ≥Grade 3 AE incidence exceeded 10%. Observed

toxicities were consistent with taxane administration, but a small P-alone sample limits conclusive toxicity comparisons between E+P and P alone.

491P PHARMACOKINETICS OF SUNITINIB IN PATIENTS WITH SEVERE RENAL IMPAIRMENT OR END STAGE RENAL DISEASE ON HEMODIALYSIS

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Sunitinib malate (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R, and RET, approved multinationally for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. This study assessed the pharmacokinetic (PK) profile of sunitinib and its primary active metabolite (SU12662) in patients with severe renal impairment and end-stage renal disease (ESRD) requiring hemodialysis.

This open-label, parallel-group study enrolled 24 patients. Patients with normal renal function (n=8, CL_{cr}>80mL/min), severe renal impairment (n=8, CL_{cr}<30 mL/min) and ESRD (n=8) requiring hemodialysis were given a single oral dose of sunitinib 50 mg. Serial blood samples were collected over 480 hours for quantification of plasma concentrations of sunitinib and SU12662 using a validated LC/MS/MS assay. For ESRD patients, the 48 hour PK blood sample was taken prior to hemodialysis. Adverse event (AE) monitoring occurred throughout the study.

All 24 patients completed the study. The mean±SD PK parameters for sunitinib are presented below.

	Normal (N=8)	Severe (N=8)	ESRD (N=8)
C _{max} , ng/mL	26±7	25±10	16±3
AUC ₀₋₄₈ , ngxh/mL	809±58	764±322	489±97
AUC _{0-∞} , ngxh/mL	1921±531	1814±1091	1013±290
t _{1/2} , h	83±12	84±20	72±17

Similar data were obtained for SU12662 and updated data will be shown for sunitinib and SU12662 at the meeting. Sunitinib was well tolerated when administered to patients with severe renal impairment or ESRD. All AEs reported were Grade 1/2 with the exception of one Grade 3 AE (headache, not treatment related) in a patient with severe renal impairment. There were no Grade 4 AEs, serious AEs, or deaths reported.

The PK profile of sunitinib and its active metabolite, SU12662, in patients with severe renal impairment was similar to that in patients with normal renal function. Patients with ESRD on hemodialysis had lower plasma levels of sunitinib and SU12662 than patients with severe renal impairment or normal renal function.

492P RELATIVE ORAL BIOAVAILABILITY OF THE HYDROGEN SULPHATE (HYD-SULFATE) CAPSULE AND FREE BASE SUSPENSION FORMULATIONS OF AZD6244 (ARRY-142886): A PHASE I TRIAL IN PATIENTS WITH ADVANCED CANCER

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Background: AZD6244 is a potent, selective, uncompetitive inhibitor of MEK1/2 being tested in phase II clinical trials for a number of solid tumours. To date, clinical trials have studied a free base oral suspension formulation, with a maximum tolerated dose (MTD) of 100mg BID. A solid oral formulation, incorporating the Hyd-Sulfate salt of AZD6244, has been developed to enable more convenient dosing. In Part A, the MTD of the AZD6244 Hyd-Sulfate formulation was identified as 75mg BID. Here we report the results from Part B of the study, which is investigating the relative bioavailability of the two formulations.

Methods: In Part B of this study, 28 patients with advanced cancer were randomised to receive a single dose of either 75mg Hyd-Sulfate or 100mg free-base formulation. These doses were the MTD for each formulation, respectively. After 7 days of washout, patients received a single dose of the alternative formulation. Post-dose on Days 1 and 8, plasma pharmacokinetic (PK) samples were collected at frequent time points over 24 hours. After the last PK sample on Day 8, patients received AZD6244 Hyd-Sulfate 75mg BID until meeting a discontinuation criterion.

Results: Preliminary analysis of the PK data indicates that for the vast majority of patients the C_{max} and AUC values for the 75mg Hyd-Sulfate solid oral formulation are

at least as high as those for the 100mg free base oral suspension. The preliminary geometric mean (CV%) C_{max} and $AUC_{0-8\text{h}}$ are 1307 (76.3) ng/mL and 4742 (34.1) ng.h/mL, and 523 (91.1) ng/mL and 2559 (66.6) ng.h/mL for the 75mg Hyd-Sulfate solid oral formulation and 100mg free base oral suspension, respectively. The safety profile of AZD6244 Hyd-Sulfate is broadly consistent with that of the free-base formulation. Further data will be presented on the relative bioavailability, clinical response and safety profile.

Conclusions: The AZD6244 Hyd-Sulfate solid oral formulation is a viable alternative to the AZD6244 free base oral suspension formulation for use in future clinical studies, based on a comparison of the PK and safety profile.

493P

A RANDOMIZED PHASE II TRIAL OF THE NOVEL POLO-LIKE KINASE 1 INHIBITOR BI 2536 IN CHEMONAÏVE PATIENTS WITH UNRESECTABLE ADVANCED PANCREATIC CANCER: A STUDY IN COOPERATION WITH THE CESAR NETWORK OF INVESTIGATORS

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Introduction: BI 2536 is a novel, potent and highly specific inhibitor of the mitotic kinase polo-like kinase-1 (Plk-1). The efficacy of BI 2536 administered in two dosing schedules was assessed in a Phase II study in chemo-naïve patients suffering from advanced or metastatic pancreatic cancer (PC).

Methods: Patients were randomized to one of two regimens: Arm A, BI 2536 200 mg i.v. q21d (1-day schedule; ODS); Arm B, BI 2536 60 mg i.v. for 3 days, q21d (3-day schedule; TDS), with an aim to enrol 35 patients in each arm. An interim analysis (IA) was planned focussing on clinical benefit defined as disease stabilization (objective response or stable disease) after 12 weeks of therapy. This IA was assessed in the first 18 eligible patients in each arm; patients with <2 cycles of therapy were ineligible.

Results: 79 patients were recruited (40/39 patients, ODS/TDS). Half of the study population (53%/46%) had moderately-differentiated, and a quarter (23%/26%) poorly-differentiated, tumours. A total of 15/17 patients (38%/44%) had extensive metastases besides liver and lung. In both arms, 5/18 eligible patients showed the clinical benefit mandated for further accrual. 41 patients (21/20) did not meet the eligibility criteria for the IA, mostly due to early progression (18/19 patients); in 3/1 patients due to symptoms likely related to progressive disease (PD). In total 65 patients (33/32) experienced PD before 12 weeks of therapy. No objective response was observed. The incidence of adverse events (AEs) was similar for ODS and TDS; most frequent AEs were fatigue (47%), nausea (43%) and neutropenia (38%). Grade 3/4 AEs were mainly haematological (drug-related) or gastrointestinal (Grade 3 only, mostly unrelated). 11 deaths have been reported; none were drug-related, and most were due to PD.

Conclusion: The trial met pre-specified criteria of the planned efficacy interim analysis. Given the high rate of early progression and the lack of objective responses in first-line therapy, further development of BI 2536 monotherapy is not warranted in pancreatic cancer patients.

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CLINICAL DEVELOPMENT OF ST1968, A NOVEL CAMPTOTHECIN DERIVATIVE WITH HIGH ANTITUMOR ACTIVITY. PRECLINICAL AND PRELIMINARY CLINICAL DATA

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Background: ST1968 is a new water-soluble camptothecin analogue extensively evaluated in preclinical models and currently under clinical development.

Methods: ST1968 in vivo antitumor activity was compared with irinotecan and/or topotecan in several human sensitive and resistant tumor xenografts including ovarian,

colon, pancreatic carcinoma, H&N, SCLC, NSCLC and mesothelioma.

Toxicological, pharmacokinetic (PK) and metabolism studies were conducted in rodents and dogs after single and repeated I.V. administrations. A phase I trial in patients (pts) with solid tumors is currently ongoing to define the Maximum Tolerated Dose (MTD) and the Recommended Dose (RD), the safety and the PK profile at cycle one.

Results: In preclinical studies I.V. ST1968 showed high efficacy against tumors sensitive and/or resistant to as well as poorly responsive to irinotecan and topotecan. ST1968 was highly active against HCT-116 colon carcinoma, NCI-H69 SCLC, A431 skin and FaDu H&N, with improved activity vs irinotecan. PK was linear. ST1968 was poorly metabolized in vitro by rat, dog, monkey and human microsomes. Target organs for toxicity were bone marrow and gastrointestinal tract. Starting dose calculation was based on the 2005 FDA guidelines. The corresponding starting dose was 2.5 mg/day and an accelerated dose escalation design was applied. The drug is administered IV as a flat dose, once a week (wk), for 2 consecutive wks, every 3 wks. As of March 2008, 18 pts have been enrolled, 4 dose levels have been evaluated, with a 5th dose level (20 mg/day) currently under evaluation. Hematological toxicity grade 3 and 4 was observed in pts at 15mg/day and 20 mg/day with no DLTs.

Conclusions: ST1968 shows an improved therapeutic index and significant antitumor activity in preclinical models. The apparent lack of any significant metabolism prompted also the clinical development of this compound which is ongoing.

495P

METRONOMIC ORAL VINORELBINE IN PATIENTS WITH RECURRENT BREAST, PROSTATE OR NON-SMALL CELL LUNG CANCER: OPTIMAL DOSE-FINDING TRIAL OF THE HELLENIC COOPERATIVE ONCOLOGY GROUP

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Purpose: Metronomic is a novel dosing strategy of cancer chemotherapy which involves regular/frequent administration of minimally toxic doses of cytotoxic drugs over protracted periods with the aim to inhibit proliferation of activated endothelial cells of tumor vasculature. Having established [EORTC-NCI-AACR 2006] a safe dose-range for metronomic application of oral vinorelbine (MOV) we ran this trial to define the optimal dose.

Methods: This was a multi-institutional randomized open-label trial [NCT00278070]. Pts with recurrent, pretreated metastatic breast (BC), prostate (PC) and non-small cell lung cancer (NSCC) were randomized to receive 30, 40 or 50 mg MOV (Navelbine®) three times a week [Mon-Wed-Fri]. Treatment continued until disease progression or toxicity grade >2 or withdrawal. Blood samples were collected for serial assessment of angiomodulating peptides VEGF, TSP-1, FGF2, IL-8, endothelial transcripts and pharmacokinetics. Differences in time-to-treatment failure (TTF), progression-free survival (PFS), toxicity, biomarkers and pharmacokinetics between the three dose levels were evaluated.

Results: Seventy-one patients enrolled from Jan 2006 to Dec 2007 (20BC, 22PC 29NSCLC). The median TTF in the 30, 40 and 50 mg dose-arms was 2, 2.3 and 1.9 months respectively and toxicity was mild. (Tab 1) The 6-month PFS rate in this pretreated population was 45% in BC, 20% in PC and 29% in NSCLC and objective antitumor effect was observed in the three arms. PK data confirmed those collected in the first part of the study that used to select the current dose levels. Low baseline levels of IL-8 and FGF2 and on treatment increase of TSP-1 mRNA and protein were associated with a favorable outcome to therapy.

Conclusion: MOV is a promising low-toxic cancer therapy with antiangiogenic potential which warrants further testing in combinations with standard-dosed chemotherapy and targeted therapeutics. Doses of 40 and 50 mg seem to be optimal. Table 1 MOV toxicity, N (%).

Grading	30 mg (N=26)			40 mg (N=24)			50 mg (N=21)		
	Gr2	G3	Gr4	G2	Gr3	Gr4	Gr2	Gr3	Gr4
Hb	2 (8)	1 (4)	-	2 (8)	-	-	-	-	-
Neutrophils	1 (4)	2 (8)	1 (4)	1 (4)	1 (4)	2 (8)	-	1 (5)	1 (5)
Platelets	3 (12)	-	-	1 (4)	-	-	-	-	-
Neuropathy	-	-	-	-	-	-	-	-	-

496P FIRST IN-MAN STUDY OF A NOVEL NUCLEOSIDE ANALOGUE, CP-4126, IN PATIENTS WITH ADVANCED SOLID TUMOURS

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Background: CP-4126 (gemcitabine 5'-elaidic acid ester) is a novel nucleoside analogue with proven preclinical antitumour activity. Unlike gemcitabine, the intracellular uptake of CP-4126 is independent of nucleoside transporters. In addition, CP-4126's preclinical antitumour activity is less affected by multidrug resistance than gemcitabine. The aim of this study is to determine the MTD and the RD of CP-4126, to investigate its safety profile and pharmacokinetic (PK) characteristics, and to preliminary assess its antitumour activity.

Material & Methods: Patients (pts) with confirmed solid tumour diagnosis are enrolled in this dose escalation study (1-6 pts per dose level (DL)). CP-4126 is administered on days (d) 1, 8 and 15 every 4 week by a 30 min IV infusion. Start dose was 30 mg/m²/d and the dose was increased by 100% until toxicity > CTCAE grade 2 occurred. Standard haematological, biological and clinical DLT definitions are used. Activity is assessed at the end of every 2nd cycle (cy). PK is determined at d1 (24 hrs) of cy 1.

Results: 26 pts have been included, with 1 pt/DL from 30 to 240 mg/m²/d. The first grade 2 AE (neutropenia) was reported at 480 mg/m²/d. Accrual is ongoing at 1600 mg/m²/d (DL9). Two DLTs are reported. One at 800 mg/m²/d; d8 treatment postponed by more than 2 weeks due to reduction in Hb and platelets (CTCAE grade 3); and one at 1000 mg/m²/d; pt died 48 hrs after treatment start due to acute lung damage. A total of 59 cycles (range 1 to 6) of treatment have been administered. The main adverse reactions have been nausea, vomiting, fatigue and anorexia, the majority of mild severity (grade 1-2). 22 pts have been withdrawn; 15 due to progressive disease; 5 due to pts or investigators decision, and 2 due to DLTs. Meaningful stabilisation of disease seen in 4 pts (colorectal and ovarian cancer) lasting between 3.5 to 6+ months (2 pts still ongoing). PK: dFdc and CP-4126 are detected in plasma up to 8 and 24 hrs, respectively.

Conclusions: MTD is not reached. Accrual is ongoing at 1600 mg/m²/d. Updated results including PK will be presented.

497P PROSPECTIVE VALIDATION OF A PROGNOSTIC SCORE FOR PATIENTS TREATED IN PHASE-I TRIALS

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Background and aims: Phase I trials are designed primarily to evaluate the tolerability and toxicity profile of new therapies. However the identification of the appropriate patient population in order to ensure safety and minimize risk remains challenging. We recently presented retrospective data on more than 200 patients (pts) who had been treated in Phase I trials (Arkenau et al, Br J Cancer 2008). We had identified albumin (<35g/l), LDH>UNL and >2 sites of metastasis as independent negative prognostic factors defining a risk score able to identify a group (score 2-3) with poor prognosis. In this study our aim was to confirm that validity of this score, by collecting information on a further group of patients treated prospectively in our institution.

Patients and methods: Based on our earlier data, we expected a median overall survival (OS) of 41 weeks for the good prognosis group with a hazard ratio (HR) of 2.3. We estimated that a cohort of 78 patients was necessary to validate the prognostic score with 90% power. We therefore identified 78 unselected patients who were treated in our institution from March 2007 to July 2007. The Kaplan-Meier method and Log-rank test was used to evaluate the OS differences in the univariate analysis and Cox Regression to calculate the HR in the multivariate analysis.

Results: The prospective cohort had a median age of 56 years (range 18-79) with a female/male ratio of 1.2:1. After a median follow-up of 16.7 weeks, the median OS was 27.1 weeks. 43 pts with a risk score of 0-1 had an OS of 33 weeks (95%CI: 24.3-41.6) and 35 pts with 2-3 had 15.7 weeks (95%CI: 10.6-20.8), p=0.036. Multivariate analysis confirmed that the risk score was an independent factor predicting OS with a HR of 1.4 (95%CI: 1.02-1.88). Moreover, for pts who had a risk score of 0 the median time of OS has not been reached yet. In contrast OS for pts with a risk score of 1, 2 or 3 was 25.7 (95%CI: 20.2-33.2), 15.7 (95%CI: 10.4-21.0) and 14.1 (95%CI: 5.9-22.3) respectively, p=0.017.

Conclusions: Prospective validation of our retrospectively derived prognostic score based on objective markers (albumin, LDH and number of metastatic sites) argue for its use as a novel, objective tool to aid patient selection for Phase I trials.

498P VACCINATION OF CLL PATIENTS WITH AUTOLOGOUS DENDRITIC CELLS LOADED WITH APOPTOTIC BODIES (APO-DC): A PHASE I-II CLINICAL TRIAL

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Background: In preclinical studies we showed that dendritic cells (DC) that have endocytosed apoptotic CLL cells (Apo-DC) are a suitable antigen presentation platform to stimulate multiple-epitope autologous antileukemic immune responses. We validated a method for large-scale production of Apo-DC from a single leukapheresis product. DC were generated from immunomagnetically enriched monocyte precursors, cultured ex vivo with GM-CSF and IL-4 and loaded with autologous apoptotic leukemic cells as antigen source.

Materials and Methods: CLL patients with slowly increasing leukemic cell count but no expected (> 6 mo) need of antitumor therapy, receive 10⁷ Apo-DC at five immunizations timepoints (wk 0, 2, 4, 6, 14). Three cohorts are accrued stepwise. Cohort I received Apo-DC alone; Cohort II: Apo-DC + GM-CSF 75 µg/day dd 1-4; Cohort III: same schedule as Cohort II + cyclophosphamide 300 mg/m² i.v. at day -2 at week 0, 6 and 14. The total period of clinical and immunological follow-up is 52 weeks. A positive immune response is defined as a ≥ 2-fold increase compared to pre-immunization values in either a proliferation or an ELISpot assay, at ≥ 2 different time points.

Results: To date, cohort I and II have been completed. The Apo-DC vaccine was well tolerated. Local, transient grade I skin reactions were observed following GM-CSF administration. The clinical and immune responses are reported in the following table:

Pt #	Schedule	Follow-up (wks)	Clinical outcome	Immune response
#01	Apo-DC	52	SD	+
#02	Apo-DC	40	PD	-
#08	Apo-DC	40	PD	-
#09	Apo-DC	52	SD	-
#12	Apo-DC	52	SD	+
#17	Apo-DC + GM-CSF	52	PD	+
#19	Apo-DC + GM-CSF	48	SD	+
#20	Apo-DC + GM-CSF	52	SD	-
#21	Apo-DC + GM-CSF	52	SD	-
#22	Apo-DC + GM-CSF	52	PD	-

Conclusions: Our results demonstrate that it is feasible to enrich monocyte precursors and generate Apo-DC for vaccine production from patients with even high leukemic cell counts. No significant toxicity was associated with this therapeutic approach. Immune responses were noted in 4/10 pts and at a 1-year follow-up 6/10 pts were clinically stable. These data indicate that the Apo-DC vaccine likely gave a clinical benefit to patients who were expected to need antitumor therapy in a lapse of time shorter than 1 year.

499P NVP-AEW 541 INHIBITS IGF-1R DRIVEN PROLIFERATION IN BILIARY TRACT CARCINOMA CELL LINES

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Background: Biliary tract cancer is associated with a poor prognosis due to wide resistance to chemotherapeutic agents and radiotherapy. Insulin-like growth factor-1 receptor (IGF-1R) is a multifunctional, membrane associated tyrosine kinase that is mitogenic, protects normal and tumor cells from apoptosis and plays an important role in supporting cellular transformation by different viral and cellular oncoproteins. NVP-AEW541, a small molecular inhibitor of IGF-1R, may be a novel treatment alternative for biliary tract cancer.

Methods: Cell-growth inhibition by NVP-AEW541 alone or combined with gemcitabine or 5-Fluorouracil (5-FU) was studied in vitro in 5 human cholangiocarcinoma and 2 gallbladder cancer cell lines. In addition, anti-tumoral drug mechanism was assessed by immunoblotting for IGF-1R, Phospho-IGF-1R, AKT, Phospho-AKT, p42/p44, Phospho-p42/p44, Stat3, Phospho-Stat3, and Bcl-xL, cell cycle analysis and RT-PCR for IGF-1R ligands IGF-1 and IGF-2.

Results: In vitro treatment suppressed the growth of all cancer cell lines with a mean IC50 (3d) of 0.51 µM and a mean IC50 (6d) of 0.22 µM, respectively. Treatment with NVP-AEW541 was associated with dephosphorylation of IGF-1R, AKT, p42/p44, Stat3 and a decrease in antiapoptotic factor Bcl-xL. In addition, treated cells showed cell cycle arrest at the G1/S-checkpoint, while the sub-G1 peak (apoptotic fraction) increased only slightly. Moreover, IGF-1R and its ligands IGF-1 and IGF-2 were

co-expressed, suggesting an autocrine loop of tumor cell activation. Combined with gemcitabine, NVP-AEW541 exerted synergistic effects, particularly in low concentrations, while results in combination with 5-FU were only additive.

Conclusions: Our findings suggest that NVP-AEW541 is active against biliary tract cancer in vitro. In addition, the compound potentiated the efficacy of gemcitabine. Based on this data, further preclinical and clinical evaluation of this new drug for the treatment of biliary tract cancer is recommended.

500P UGT1A1*6 AND UGT1A1*27 ARE ASSOCIATED WITH IRINOTECAN-INDUCED SEVERE NEUTROPENIA IN JAPANESE PATIENTS WITH NSCLC

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Purpose: Genetic polymorphisms of the UDP-glucuronosyltransferase 1A1 (UGT1A1), UGT1A7, and UGT1A9 genes confer individual differences in the efficacy and toxicities of irinotecan. Thus, we investigated whether these genetic polymorphisms were associated with the toxicities in Japanese patients with previously untreated non-small cell lung cancer (NSCLC) enrolled in the randomized phase II trial of irinotecan combination regimens.

Patients and methods: In this trial, 77 patients with previously untreated NSCLC were randomly assigned to either irinotecan plus paclitaxel (arm A; n = 37) or irinotecan plus gemcitabine (arm B; n = 40). The patients with NSCLC were divided into the following two subgroups: those with (grade 4) or without toxicities, according to NCI-CTC. Genomic DNA was extracted from peripheral blood of each patient after written informed consent was obtained. The polymorphisms of UGT1A1 (UGT1A1*6, UGT1A1*27), UGT1A7 (UGT1A7*), and UGT1A9 (UGT1A9*22) were detected by the PCR-direct DNA sequence. UGT1A1*28 was detected by polyacrylamide gel electrophoresis method, and UGT1A1*60 was detected by Taq-Man[®] PCR method. The frequencies and distributions of genotypes in these genes were compared between the subgroups of these patients by Wald test.

Results: Our results indicated that UGT1A1*6 and UGT1A1*27 polymorphisms were associated with the susceptibility to irinotecan-induced grade 4 neutropenia, although UGT1A1*28 was not associated with this toxicity. Additionally, there were no significant differences in frequencies of other polymorphisms between the patients with and without toxicities including diarrhea.

Conclusions: The present study indicates an association between UGT1A1*6 and UGT1A1*27 and severe neutropenia in Japanese patients with irinotecan-treated NSCLC. These polymorphisms of UGT1A1 could therefore be potentially applied to DNA-based diagnosis before chemotherapy in NSCLC patients as a risk biomarker for predicting the severe neutropenia.

501 A PHASE I STUDY OF VORINOSTAT IN JAPANESE PATIENTS WITH GASTROINTESTINAL (GI) CANCER

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Background: Vorinostat (Zolinza[®]) is an inhibitor of histone deacetylases with clinical activity in patients with various types of cancer including cutaneous T-cell lymphoma. The objectives of this study were to investigate the safety, clinical activity, and pharmacokinetic (PK) profile of vorinostat in Japanese patients with GI cancer.

Methods: Japanese patients with GI cancers who had failed standard therapy were enrolled into 2 dose levels that were recommended doses used outside Japan. In a 21-day cycle, vorinostat was administered at 300 mg BID for 3 consecutive days followed by a 4-day rest (level 1), and was escalated to 400 mg QD continuous (level 2) for the safety evaluation. PK and response were also assessed.

Results: All 16 enrolled patients had GI cancer: 10 gastric cancer, 3 rectal cancer, and 3 colon cancer. 10 patients received vorinostat at dose level 1, and 6 at dose level 2. Median (range) age was 58 yrs (32-73) and number of prior regimens was 4 (2-6). All patients were included in the safety assessment, while 1 patient was excluded from PK assessment due to incomplete dose received on Day 1. At level 1, no patients experienced dose-limiting toxicity (DLT). At level 2, 2 patients developed Grade 4 thrombocytopenia as DLT, and 1 patient developed a non-DLT of Grade 3 thrombocytopenia, during cycle 1. Although the PK profiles were generally consistent with results in a previous Phase I study (ASCO2007 Abs#14015), the 3 patients in level 2 showed higher exposure, which was clinically and pharmacologically meaningful, compared with the previous data on 400 mg QD in Japanese patients with solid tumors. All ≥Grade 3 drug-related adverse events, which were thrombocytopenia (31.3%) and anemia (6.3%), resolved with supportive therapy. Of the 16 patients enrolled, 8 achieved stable disease (SD) as best response. Median duration of SD was 3.4 months. Of the 8 patients with gastric cancer who received vorinostat at level 1, 3 achieved SD for >4.0 months, including 1 patient who maintained SD for 8.1 months. The study was complete as of October 2007.

Conclusions: This study demonstrates that 300 mg BID for 3 consecutive days followed by a weekly 4-day rest was a tolerable dose regimen for Japanese patients with GI cancer based on safety and PK results.

502 METRONOMIC CHEMOTHERAPY (MC) WITH ORAL URACIL/TEGAFUR (UFT), CYCLOPHOSPHAMIDE (CTX) AND CELECOXIB IN PRETREATED PATIENTS WITH ADVANCED GASTROINTESTINAL CANCERS: A PILOT CLINICAL STUDY WITH PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) EVALUATIONS

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Background: MC (long term, low dose, frequent administration) produces an antineoplastic effect through an angiogenic inhibition in vitro and in vivo and an antitumor activity in clinical studies. The antitumor effect of a MC with CTX is due to an increase of thrombospondin-1 (TSP-1) plasma level, an endogenous inhibitor of angiogenesis. The rationale of a MC with UFT and CTX derives from an observed synergistic antitumor activity of the combination in vivo experimental mouse model.

Methods: the primary aim was to demonstrate that a MC with UFT, CTX and celecoxib produced an increase in the progression free survival (PFS) from 50% to 70% at two months in a population of heavily pre-treated patients with advanced gastrointestinal cancers; secondary objectives were: the response rate, the safety profile, a PD evaluation of anti- and pro-angiogenic factors, such as the TSP-1 and the vascular endothelial growth factor (VEGF) and a PK analysis of the 5-FU, uracil and tegafur. This MC regimen consisted of a daily oral administration of UFT 100mg bid, CTX 50mg and celecoxib 200mg bid until disease progression.

Results: up today 26 patients (18 colorectal, 3 pancreatic, 4 biliary tracts, 1 gastric) entered the study. Patients characteristics were: M/F = 17/9, median age = 69 years (range 59 - 87); PS 0/1/2 = 7/16/3; sites of disease (single/multiple) = 6/20; median of previous lines of chemotherapy: 3 (range 1 - 8). 190 weeks of therapy were administered and the median number of weeks was 10 (range 2-24). No toxicities of grade >1 (NCI scale) were observed. 18 patients were assessable for response: 5 patients (19%) obtained a stable disease with a median duration of 14 weeks (range 12 - 20). The median time to PFS was 2.5 months (range 1-4).

Conclusions: preliminary results demonstrated that the MC with UFT, CTX and celecoxib was feasible. Pharmacodynamic effects and pharmacodynamic analysis of the combination was still ongoing. Supported by A.I.R.C.